03-04-06

AF

DOCKET NO.: AM101201/WYNC-0325 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:
Deborah Ann Evrard, *et al.*

Confirmation No.: 4846

Application No.: 10/659,537

Group Art Unit: 1624

Filing Date: September 10, 2003

Examiner: Emily B. Bernhardt

For: Antidepressant Arylpiperazine Derivatives of Heterocycle-Fused Benzodioxans

EXPRESS MAIL LABEL NO: EV 765640727 US
DATE OF DEPOSIT: March 8, 2006

EV765640727US

MS Appeal Brief - Patent
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL PURSUANT TO 37 CFR § 1.192

Transmitted herewith is the APPEAL BRIEF in this application with respect to the Notice of Appeal received by The United States Patent and Trademark Office on **January 9, 2006**.

☐ Applicant(s) has previously claimed small entity status under 37 CFR § 1.27 .

☐ Applicant(s) by its/their undersigned attorney, claims small entity status under 37 CFR § 1.27 as:

- ☐ an Independent Inventor
- ☐ a Small Business Concern
- ☐ a Nonprofit Organization.

☐ Petition is hereby made under 37 CFR § 1.136(a) (fees: 37 CFR § 1.17(a)(1)-(4) to extend the time for response to the Office Action of to and through comprising an extension of the shortened statutory period of month(s).

	SMALL ENTITY		NOT SMALL ENTITY	
	RATE	FEE	RATE	FEE
☒ APPEAL BRIEF FEE	$250	$	$500	$500
☐ ONE MONTH EXTENSION OF TIME	$60	$	$120	$
☐ TWO MONTH EXTENSION OF TIME	$225	$	$450	$
☐ THREE MONTH EXTENSION OF TIME	$510	$	$1020	$
☐ FOUR MONTH EXTENSION OF TIME	$795	$	$1590	$
☐ FIVE MONTH EXTENSION OF TIME	$1080	$	$2160	$
☐ LESS ANY EXTENSION FEE ALREADY PAID	minus	($)	minus	($)
TOTAL FEE DUE		$0		$500

☒ The Commissioner is hereby requested to grant an extension of time for the appropriate length of time, should one be necessary, in connection with this filing or any future filing submitted to the U.S. Patent and Trademark Office in the above-identified application during the pendency of this application. The Commissioner is further authorized to charge any fees related to any such extension of time to Deposit Account 23-3050. This sheet is provided in duplicate.

☐ A check in the amount of **$ .00** is attached. Please charge any deficiency or credit any overpayment to Deposit Account No. 23-3050.

☒ Please charge Deposit Account No. 23-3050 in the amount of **$500.00**. This sheet is attached in duplicate.

☒ The Commissioner is hereby authorized to charge any deficiency or credit any overpayment of the fees associated with this communication to Deposit Account No. 23-3050.

Date: March 8, 2006

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DOCKET NO.: AM101201 /WYNC-0325 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: **Deborah Ann Evrard, *et al.*** Confirmation No.: **4846**

Serial No.: **10/659,537** Group Art Unit: **1624**

Filing Date: **September 10, 2003** Examiner: **Bernhardt, Emily B.**

For: **Antidepressant Arylpiperazine Derivatives of Heterocycle-Fused Benzodioxans**

EXPRESS MAIL LABEL NO: EV765640727 US
DATE OF DEPOSIT: March 8, 2006

Mail Stop Appeal-Brief Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

APPELLANT'S BRIEF PURSUANT TO 37 C.F.R. § 41.37

This brief is being filed in support of Appellant's appeal from the final rejection of claims 1 to 10 and 49 to 52 mailed July 26, 2005. A Notice of Appeal was filed on January 9, 2006.

1. REAL PARTY IN INTEREST

The real party in interest is Wyeth, 500 Five Giralda Farms, Madison, NJ 07940, by virtue of the assignment recorded September 3, 2004.

2. RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending. See appendix entitled RELATED PROCEEDINGS APPENDIX.

3. STATUS OF CLAIMS

Pending	:	Claims 1 to 52
Rejected	:	Claims 1 to 5, 7 to 10, and 49 to 52
Objected to	:	Claims 6 and 11 to 48
Allowed	:	None
Withdrawn	:	None
Appealed	:	Claims 1 to 5, 7 to 10, and 49 to 52.

The claims are listed in the appendix entitled CLAIMS APPENDIX.

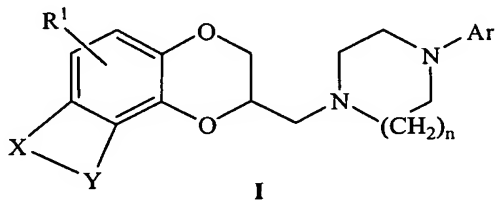
4. STATUS OF AMENDMENTS

The Amendment after Final Rejection, filed October 24, 2005, was entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention relates generally to arylpiperazine derivatives of heterocycle-fused benzodioxans (claims 1 to 48; page 2, **[0010]** to page 22, **[0043]**, page 29 [0059] to page 71 **[0143]**), methods of use thereof (claim 49; page 24, **[0044]** to page 26, **[0049]**), and pharmaceutical compositions thereof (claim 52; page 27, **[0050]** to page 28, **[0054]**).

Claim 1 and its dependent claims 2 to 16 and 18 to 48, as set forth in the CLAIMS APPENDIX, are directed to compounds of the formula I:



I

page 2, **[0010]** to page 22, **[0043]**, page 29 [0059] to page 71 **[0143]**.

Claim 49 is directed to a method of treating a subject suffering from a condition selected from depression, anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder, obesity, eating disorders, vasomotor flushing, alcohol addiction, and sexual dysfunction, comprising the step of:

providing to said subject suffering from said condition, a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

page 24, **[0044]** to page 26, **[0049]**.

Claim 52 of the instant application is directed to a pharmaceutical composition comprising an effective amount of a compound of the formula I (or a pharmaceutically effective salt thereof) and a pharmaceutically acceptable carrier or excipient. See page 27, **[0050]** to page 28, **[0054]**.

The compounds of formula I are combined selective serotonin reuptake inhibitors (SSRIs) and 5-HT_{1A} serotonin receptor antagonists. Appellant has demonstrated that the compounds of formula I have SSRI activity through an art-recognized assay (page 24, paragraph 44). The appellant has also demonstrated that the compounds of formula I have 5-HT_{1A} serotonin receptor antagonist activity through two art-recognized assays (page 24, paragraphs 45 and 46). The first 5-HT_{1A}-antagonist assay is the ^{3}H-paroxetine binding assay, which assesses affinity of drugs for the serotonin transporter. The second assay assesses the agonism/antagonism at the 5-HT_{1A} receptor using [^{35}S]-GTPγS binding to cloned human 5-HT_{1A} receptors. Appellant has also provided data to show that representative compounds of formula I have potent affinity for and antagonist activity at brain 5-HT_{1A} serotonin receptors (page 25).

As combined selective serotonin reuptake inhibitors and 5-HT_{1A} serotonin receptor antagonists, the compounds of formula I are expected to be useful in the treatment of, *inter alia*, depression, anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive-compulsive disorder, social anxiety disorder, generalized anxiety disorder, obesity, eating disorders, vasomotor flushing, alcohol addiction, and sexual dysfunction (page 26, **[0048]**). Claims 49 to 51 are directed to methods

for treating such conditions through the administration of a therapeutically effective amount of a compound according to the formula I.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 1 to 5, 7 to 10, and 49 to 52 are unpatentable under 35 U.S.C. § 112, first paragraph, as being based on a non-enabling disclosure.

7. ARGUMENT

It has not been prima facie established that claims 1 to 5, 7 to 10, and 49 to 52 are not enabled under 35 U.S.C. § 112, first paragraph

In order to establish a *prima facie* case of non-enablement, the following must be established by the Patent Office:

1. a rational basis as to
    a. why the disclosure does not teach; or
    b. why to doubt the objective truth of the statements in the disclosure that purport to teach;
2. the manner and process of making and using the invention
3. that correspond in scope to the claimed invention
4. to one of ordinary skill in the pertinent technology,
5. without undue experimentation, and
6. dealing with subject matter that would not already be known to the skilled person as of the filing date of the application.

Any rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement, must include evidence supporting each of these elements. Appellant respectfully submits that the Office has failed to meet its burden of establishing a *prima facie* case of non-enablement.

It has been consistently held that the first paragraph of 35 U.S.C. § 112 requires nothing more than *objective* enablement. Furthermore, a specification that teaches how to make and use the invention in terms that correspond in scope to the claims *must* be taken as complying with the first paragraph of 35 U.S.C. § 112, *unless* there is reason to doubt the objective truth of the statements relied upon therein for enabling support. *Stahelin v. Secher*, 24 U.S.P.Q.2d 1513, 1516 (B.P.A.I. 1992) (citing *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (C.C.P.A. 1971)). "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to ... back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971). It is the position of appellant that the Office has not provided even a modicum of *objective, technical evidence* that the claimed genus of compounds do not have SSRI/$5HT_{1A}$-antagonist activity, and therefore that the Office has not met its burden of proof with respect to its contention of non-enablement pursuant to 35 U.S.C. § 112, first paragraph.

In the instant application, the Office alleges that adequate substantiation has been provided to support its enablement rejection. In particular, the Office states that "reasoning, evidence...and case law have been provided to support the enablement rejection." *See* Advisory Action Before the Filing of an Appeal Brief (hereafter "Advisory Action"), 11/18/2005, at page 2. However, while the Office does cite to abstracted doctrinal

propositions relating to enablement both in general and in the context of chemical inventions, it is of critical importance to note that the Office has still neglected to provide objective reasoning as to why *the present invention* and the disclosure therefor are fatally defective in terms of enablement.

More particularly, citation to the generalized pronouncements of such cases as *In re Cavillito*, 282 F.2d 357 (C.C.P.A. 1960), without the provision of statements as to such cases' particular applicability to the present application, cannot suffice to meet the Office's burden to demonstrate insufficient enablement. *Cavillito* (and other like cases) would only be applicable if the Office in the instant situation had provided technical, objective reasons as to why it would be unreasonable to expect that the claimed compounds would not demonstrate the posited effects, as had the examiner in the *Cavillito* situation: in contrast with the wholly subjective and purely argumentative strategy adopted by the Office with regard to the instant application, the examiner's (and later the Board of Appeals') position in *Cavillito* was founded, *inter alia*, on the technical observation that, for example, "certain specified compounds falling within the scope of the claims contained radicals which would be expected to be antagonistic to 'the hypotensive effect that all the compounds are said to exert'". *Cavillito*, 282 F.2d at 360. Thus, the position of the applicant in *Cavillito* was *technically* flawed by virtue of the fact that the application at issue provided no indication that "compounds of the kind claimed here, containing such radicals [as are expected by those skilled in the art to be antagonistic to the claimed hypotensive effect], possessed the same hypotensive potency as those having neutral substituents." *Id.* at 362. *Cavillito* therefore stands for the proposition, against which appellant does not strive to contend, that where specified objective/technical evidence exists (as demonstrated by the Office) that members of

a claimed genus of compounds would not be expected to possess the posited effect, an enablement rejection may be justified, and the appellant would be compelled to respond with evidence to the contrary. The Office improperly cites *Cavillito* and other such cases (such as *In re Fisher*, which is addressed in the Appellant's Reply of October 25, 2005) in the present instance, where no objective evidence has been presented that would suggest that the claimed compounds do not possess any SSRI/$5HT_{1A}$-antagonist activity, and so the caselaw to which the Office refers does not support a proper *prima facie* enablement rejection, as alleged by the Office.

Likewise, as described *supra*, contrary to the suggestion of the Office, no evidence has been adduced that those skilled in the art would not consider the present disclosure to be enabling as of the filing date. First, the Office cites to MPEP § 2164.08(b) for the proposition that "significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify any of the operative embodiments and undue experimentation is involve in determining those that are operative." Such proposition is clearly inapplicable to the instant application, wherein the specification *does* clearly identify a host of operative embodiments (page 25; *see also* Appellant's argument, *infra* at 7-8), and where those embodiments for which the potency is not specifically disclosed can be routinely evaluated using the art-recognized assays that are clearly referenced in the specification (page 24). At the time the instant application was filed, it was widely recognized among those skilled in the art that the assay for determining the disclosed compounds' affinity for the 5HT transporter, the assay for the $5HT_{1A}$ receptor, and the assay for antagonist activity at the $5HT_{1A}$ receptor, as well as the synthesis schemes, dosage forms and dosage levels, and dual SSRI/$5HT_{1A}$ activity data, reasonably correlate to the effects claimed in claims 1 to 5, 7 to 10,

and 49 to 52 (*see* May 5, 2005 Reply at 14-15). Although the Office indicates its position that, supposedly pursuant to the aspect of the Wands analysis that considers the state of the prior art (*see In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988)), "there is no evidence that compounds of similar structure are known to have such activities" (Advisory Action at page 4), a proper application of the "state of the prior art" analysis should consider the awareness of those skilled in the art of the reliability and recognized utility of the disclosed assays, not whether compounds having the disclosed core structure are art-recognized as correlating to a particular effect. Appellant has submitted that the state of the art with respect to these assays may be used to conclude that the rejected claims are enabling as of the filing date. Contrary to the suggestion of the Office, a proper Wands analysis should not consider whether the knowledge of those skilled in the art at the time the instant application was filed included specific facts about compounds having the disclosed core structure. Although it is the Office's burden to do so in light of the appellant's disclosure and argument, the Office does not present evidence that those skilled in the art would not consider the present disclosure to be enabling as of the filing date, and so a *prima facie* case of non-enablement has not been established. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (C.C.P.A. 1971) ("it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure...Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.") (emphasis in original).

As provided in the communication of May 5, 2005, appellant therefore respectfully submits that because the non-enablement rejection is not supported by sufficient evidence that the compounds of the formula I and methods of their use cannot be made and used in the

manner described in the specification without undue experimentation, there is not a reasonable basis for rejecting the claims. Accordingly, appellant respectfully requests reconsideration and withdrawal of the rejection of claims 1 to 5, 7 to 10, and 49 to 52 under 35 U.S.C. § 112, first paragraph, for alleged non-enablement.

Representative examples establish that the compounds of formula I are SSRIs/5-HT_{1A} receptor antagonists

As contrasted with Office's assertion that a high degree of unpredictability exists in the SSRI/$5HT_{1A}$-antagonist art (Advisory Action, page 3), appellant submits that it has presented representative examples that establish that the compounds of formula I are SSRIs/$5HT_{1A}$ receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art. Appellant further submits that the Office's position ignores the objectively reliable character of *in vitro* assays presented in specification.

Appellant has demonstrated that representative compounds of formula I have SSRI activity through an art-recognized assay (page 24, paragraph 44). Appellant has also demonstrated that the compounds of formula I have 5-HT_{1A} serotonin receptor antagonist activity through two art-recognized assays (page 24, paragraphs 45 and 46). The first $5HT_{1A}$-antagonist assay is the ^{3}H-paroxetine binding assay, which assesses affinity of drugs for the serotonin transporter. The second assay assesses the agonism/antagonism at the $5HT_{1A}$ receptor using [^{35}S]-GTPγS binding to cloned human $5HT_{1A}$ receptors. Appellant has also provided data to show that representative compounds of formula I have potent affinity for and antagonist activity at brain $5HT_{1A}$ serotonin receptors (page 25).

Appellant submits that the skilled artisan would accept the disclosed models as reasonably correlating to the claimed effects and, as such, the Office must consider and accept the objective truth of the information unless there is *evidence* in the record to the contrary. *See In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995) (reversing the decision that *in vitro* data did not support *in vivo* applications); MPEP § 2164.02.

As discussed *supra*, it is not the absence or presence of a structural relationship between known modulators of $5HT_{1A}$ receptor activity and the compounds of the present invention that induces appellant to extrapolate the results of the known modulators of $5HT_{1A}$ receptor activity as forms of treatment for various medical conditions to the inventive compounds, but rather the *functional* relationship, *viz.*, ^{3}H-serotonin uptake inhibition as demonstrated through ^{3}H-paroxetine binding, as well as activity at the $5HT_{1A}$ receptor as demonstrated through reliable testing for ^{3}H-paroxetine binding and $5HT_{1A}$ receptor antagonism, that permits appellant to provide compounds that utilize the nexus between the modulation of serotonin uptake and $5HT_{1A}$ receptor activity and the treatment of certain serotonin- and $5HT_{1A}$ receptor-effected medical conditions.

Accordingly, appellant submits that it has presented representative examples that establish that the compounds of formula I are SSRIs and 5-HT_{1A} receptor antagonists, commensurate with the scope of the claimed genus and sufficient for the degree of predictability in the art.

It is well known in the art that SSRI activity and enhancement thereof via $5HT_{1A}$ antagonism can provide the basis for particularized therapeutic treatment as recited in claim 49

Claim 49 stands rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Because the Office declined to consider appellant's argument and submitted references with regard to the rejection of claim 49, Appellant hereby presents said argument and references for the Board's consideration.

Although the Office suggests otherwise, at the time the instant application was filed, there was documented recognition by those skilled in the art of the efficacy of SSRI drug therapy for treating the pathologies specified claim 49 of the present application. As detailed below, there is voluminous confirmation by those skilled in the art that selective serotonin reuptake inhibition, when effected through therapeutic administration of pharmacological agents, can benefit patients that suffer from the medical conditions specified in claim 49.

For example, SSRI compounds like sertraline and other SSRIs have been shown to have a broad range of efficacy in treatment of post-traumatic stress disorder (PTSD) and also alcoholism (*see* Brady KT *et al.*, "Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence," *J. Clin. Psychiatry* 56:502-5 (**1995**); attached); paroxetine has also been shown to represent effective treatment for PTSD (*see* Wagstaff AJ, *et al.*, "Paroxetine: an update of its use in psychiatric disorders in adults," *Drugs,* 62(4):655-703. Review (**2002**)); fluoxetine has been demonstrated an effective treatment for attention deficit/hyperactivity disorder (*see* Kafka MP, Hennen, J., "Psychostimulant augmentation during treatment with selective serotonin reuptake inhibitors in men with paraphilias and

paraphilia-related disorders: a case series," *J. Clin. Psychiatry*, 61(9):664-70 (**2000**); attached); escitalopram oxalate (*e.g.*, Lexapro®) has been proven efficacious and is FDA approved for treatment of generalized anxiety disorder (*see* Lexapro® package insert, page 3; attached); Boyer WF, "Potential indications for the selective serotonin reuptake inhibitors," *Int. Clin. Psychopharmacol.* 6 Suppl. 5:5-12 (**1992**) (attached) demonstrates that the common SSRI side effect of decreased appetite and subsequent weight loss appears to be most pronounced in obese patients and may be a useful effect as an adjunct to diet and exercise in cases of severe obesity; Boyer also reports that fluoxetine is an effective treatment for anorexia nervosa, an eating disorder, as well as premenstrual dysphoric disorder; fluoxetine (*e.g.*, Prozac®) is also indicated for treatment of bulimia nervosa, another eating disorder (*see* Prozac® package insert, page 8, attached); venlafaxine (*e.g.*, Effexor®), paroxetine (*e.g.*, Paxil®), sertraline (*e.g.*, Zoloft®), and fluoxetine (*e.g.*, Prozac®) have all been shown effective in treatment of vasomotor flushing (*see, e.g.*, Stearns V., *et al.*, "Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial," *JAMA*, 289(21):2827-34 (**2003**); *see also* Loprinzi, CL, *et al.*, "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial," *Lancet*, 356(9247):2059-63 (**2000**); both attached); fluoxetine has furthermore been demonstrated efficacious in treatment of alcoholism (*see* Janiri L, *et al.*, "*Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics*," *Int. Clin. Psychopharmacol.* 11:109-17 (**1996**); attached); and, paroxetine, citalopram, and other SSRIs have been used to effectively treat certain forms of sexual dysfunction. *See* McMahon CG and Touma K, "Treatment of premature ejaculation with paroxetine hydrochloride," *Int. J. Impot. Res.*, 11(5):241-245; discussion 246 (**1999**); Atmaca M, *et al.*, "The efficacy of

citalopram in the treatment of premature ejaculation: a placebo-controlled study," *Int. J. Impot. Res.*, 14(6):502-5 (**2002**), both attached.

Therefore, appellant submits that at the time the instant invention was filed, persons skilled in the art widely recognized the nexus between treatment of the specified medical conditions and the mediation of serotonin uptake via treatment with compounds identified as possessing SSRI functionality.

Furthermore, the interplay between the serotonin transporter (SERT) and the $5HT_{1A}$ receptor has been characterized by those skilled in the art, and the instant invention specifically utilizes this interplay to effect enhanced treatment for specified medical conditions. It is well-documented that reduction of negative feedback and augmentation of the serotonin reuptake mechanism can be effected by coadministration of $5HT_{1A}$ antagonists. *See* Perez, *et al.* (**1997**) (cited in IDS mailed January 27, 2004, as considered by Examiner February 7, 2005); *see also* Perez V, Puigdemont D, Gilaberte I, Alvarez E, Artigas F, "Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors," *J. Clin. Psychopharmacol.* (**2001**) Feb 21(1):36-45; attached. Thus, it is well known in the art that selective serotonin reuptake inhibition, and enhancements thereof (*e.g.,* via $5HT_{1A}$ antagonism), can provide the basis for particularized therapeutic treatment as recited in claim 49.

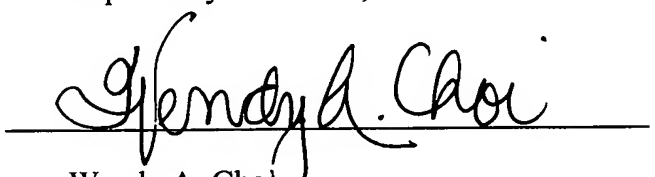
Accordingly, appellant respectfully requests reconsideration of the rejection of claim 49 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Appellant submits

that the claim, as amended, is in proper condition for allowance, and that claims 50 and 51, which depend from claim 49, are also in condition for allowance.

Conclusion

For the foregoing reasons, it is respectfully submitted that the Office has not met its burden of establishing that claims 1 to 5, 7 to 10, and 49 to 52 are not enabled under 35 U.S.C. § 112, first paragraph. Appellant, therefore, requests that this patent application be remanded to the Patent Office with an instruction to both withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph, and allow the appealed claims.

Respectfully submitted,



Date: March 8, 2006

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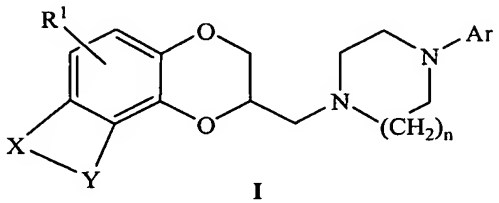
CLAIMS APPENDIX

The following claims are involved in the present appeal:

1. A compound of formula I:



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wherein

R^1 is hydroxy, halo, cyano, carboxamido, carboalkoxy of 2 to 6 carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms;

the group X—Y is $-N=C(R^2)-C(R^3)=N-$, $-N=C(R^2)-C(R^4)=CH-$, $-N=C(R^2)-N=CH-$, $-N=C(R^2)-O-$, or $-NH-C(R^5)=CH-$;

R^2 and R^3 are, independently, hydrogen, halo, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms or alkyl of 1 to 6 carbon atoms;

R^4 is hydrogen or alkyl of 1 to 6 carbon atoms;

R^5 is hydrogen, halo, trifluoromethyl, pentafluoroethyl or alkyl of 1 to 6 carbon atoms;

Ar is phenyl, naphthyl, indolyl, indazolyl, thienyl, pyridinyl, pyrimidinyl, quinolinyl, benzofuranyl, benzothienyl, benzoisothiazolyl, or benzisoxazolyl, each

optionally substituted with one to three substituents independently selected from hydroxy, halo, cyano, carboxamido, carboalkoxy of 2 to 6 carbon atoms, trifluoromethyl, alkyl of 1 to 6 carbon atoms, alkanoyloxy of 2 to 6 carbon atoms, amino, mono- or di-alkylamino in which each alkyl group has 1 to 6 carbon atoms, alkanamido of 2 to 6 carbon atoms, or alkanesulfonamido of 1 to 6 carbon atoms; and

n is 1 or 2;

or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein R^1 is hydrogen, halo, cyano, trifluoromethyl, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms.

3. A compound according to claim 1, wherein R^1 is hydrogen, halo or alkoxy of 1 to 6 carbon atoms.

4. A compound according to claim 1, wherein R^1 is hydrogen.

5. A compound according to claim 1, wherein Ar is phenyl, quinolinyl, benzofuranyl, benzothienyl, or indolyl, each optionally substituted.

6. A compound according to claim 1, wherein X-Y is $-N=C(R^2)-C(R^4)=CH-$ and R^4 is hydrogen or alkyl of 1 to 3 carbon atoms.

7. A compound according to claim 1, wherein R^2 and R^3 when present are independently selected from hydrogen, amino or alkyl of 1 to 6 carbon atoms.

8. A compound according to claim 1, wherein R^2 and R^3 when present are independently hydrogen or alkyl of 1 to 3 carbon atoms.

9. A compound according to claim 1, wherein R^5 is hydrogen, trifluoromethyl, pentafluoroethyl or alkyl of 1 to 6 carbon atoms.

10. A compound according to claim 1, wherein R^5 is hydrogen, trifluoromethyl or alkyl of 1 to 3 carbon atoms.

11. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(3-chlorophenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(4-chlorophenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

13. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(3,4-dichlorophenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4] dioxine [2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

14. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(2-methoxyphenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(3-methoxyphenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

16. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(4-methoxyphenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

17. A compound wherein said compound is (2S)-2-{[4-(dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4] dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

18. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-[4-(3-trifluoromethyl-phenyl)piperazin-1-ylmethyl]-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

19. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-[4-(3-fluorophenyl)piperazin-1-ylmethyl]-2,3-dihydro[1,4] dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

20. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(2,3-dimethylphenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

21. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(3,4-dimethylphenyl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

22. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-[(4-quinolin-2-ylpiperazin-1-yl)methyl]-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

23. A compound according to claim 1, wherein said compound is ((2S)-8-methyl-2-{4-(6-nitroquinolin-2-yl)piperazin-1-yl]methyl)-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

24. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-{4-(6-chloroquinolin-2-yl)piperazin-1-yl]methyl)-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

25. A compound according to claim 1, wherein said compound is 2-(4-{[(2S)-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinolin-2-yl]methyl}piperazin-1-yl}quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

26. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(1-benzofuran-3-yl)-1-piperazinyl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

27. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(5-fluoro-1-benzofuran-3-yl)-1-piperazinyl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

28. A compound according to claim 1, wherein said compound is ((2S)-2-{[4-(7-methoxy-1-benzofuran-3-yl)-1-piperazinyl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

29. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-{[(2S)-2-methyl-4-quinolin-2-ylpiperazin-1-yl]methyl}-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

30. A compound according to claim 1, wherein said compound is 2-((3R)-3-methyl-4-{[(2S))-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinolin-2-yl]methyl}piperazin-1-yl]quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

31. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-{[(2R)-2-methyl-4-quinolin-2-ylpiperazin-1-yl]methyl}-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

32. A compound according to claim 1, wherein said compound is (2S)-8-methyl-2-{[4-(2-naphthyl)piperazin-1-yl]methyl}-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

33. A compound according to claim 1, wherein said compound is (2S)-2-[4-8-methyl-2,3-dihydro-[1,4]dioxino[2,3-f]quinolin-2-yl)-piperazin-1-yl]-quinoline-6-carboxylic acid amide or a pharmaceutically acceptable salt thereof.

34. A compound according to claim 1, wherein said compound is (2S)-2-[4-(2,3-Dihydro-[1,4]dioxino[2,3-*f*]quinolin-2-ylmethyl)-piperazin-1-yl]-quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

35. A compound according to claim 1, wherein said compound is (2S)-2-[4-(8-Ethyl-2,3-dihydro-[1,4]dioxino[2,3-*f*]quinolin-2-ylmethyl)-piperazin-1-yl]-quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

36. A compound according to claim 1, wherein said compound is (2S)-2-[4-(2-Methyl-7,8-dihydro-1,6,9-trioxa-3-aza-cyclopenta[*a*]naphthalen-8-ylmethyl)-piperazin-1-yl]-quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

37. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-Bromoquinolin-2-yl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

38. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-Bromoquinolin-2-yl)piperazin-1-yl]methyl}-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

39. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-methoxyquinolin-2-yl)piperazin-1-yl]methyl]-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

40. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-Trifluoromethoxyquinolin-2-yl)piperazin-1-yl]methyl]-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

41. A compound according to claim 1, wherein said compound is 2-[4-(6-Fluoro-quinolin-2-yl)-piperazin-1-ylmethyl]-8-methyl-2,3-dihydro-[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

42. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-methoxyquinolin-2-yl)-1,4-diazepan-1-yl]methyl]-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

43. A compound according to claim 1, wherein said compound is 2-(4-{[(2S)-8-Methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinolin-2-yl]methyl}-1,4-diazepan-1-yl)quinoline-6-carbonitrile or a pharmaceutically acceptable salt thereof.

44. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-Trifluoromethoxy-quinolin-2-yl)-1,4-diazepan-1-yl]methyl]-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

45. A compound according to claim 1, wherein said compound is 2-[4-(6-Fluoro-quinolin-2-yl)-[1,4]diazepan-1-ylmethyl]-8-methyl-2,3-dihydro-[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

46. A compound according to claim 1, wherein said compound is (2S)-2-{[4-(6-Bromo-quinolin-2-yl)-1,4-diazepan-1-yl]methyl]-8-methyl-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

47. A compound according to claim 1, wherein said compound is 8-Methyl-2-(4-quinolin-2-yl-[1,4]diazepan-1-ylmethyl)-2,3-dihydro-[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

48. A compound according to claim 1, wherein said compound is 8-Methyl-2-[4-(4-methyl-quinolin-2-yl)-[1,4]diazepan-1-ylmethyl]-2,3-dihydro[1,4]dioxino[2,3-f]quinoline or a pharmaceutically acceptable salt thereof.

49. A method of treating a subject suffering from a condition selected from depression, anxiety, panic disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, attention deficit disorder, obsessive-compulsive disorder, social anxiety

disorder, generalized anxiety disorder, obesity, eating disorders, vasomotor flushing, alcohol addiction, and sexual dysfunction, comprising the step of:

providing to said subject suffering from said condition, a therapeutically effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof.

50. A method according to claim 49, wherein the condition is depression.

51. A method according to claim 49, wherein the condition is selected from the group consisting of obsessive-compulsive disorder, panic attacks, generalized anxiety disorder, and social anxiety disorder.

52. A pharmaceutical composition, comprising:

an effective amount of a compound according to claim 1 or a pharmaceutically acceptable salt thereof; and

a pharmaceutically acceptable carrier or excipient.

EVIDENCE APPENDIX

The references referred to in the table below are enclosed.

Condition	***Reference(s) showing nexus between SSRI activity and Condition***
Post-traumatic stress disorder (PTSD)	Brady KT *et al.*, "Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence," *J. Clin. Psychiatry* 56:502-5 (**1995**); Wagstaff AJ, *et al.*, "Paroxetine: an update of its use in psychiatric disorders in adults," *Drugs,* 62(4):655-703. Review (**2002**)
Alcoholism	Brady KT *et al.*; Janiri L, *et al.*, "Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics," *Int. Clin. Psychopharmacol.* 11:109-17 (**1996**)
Attention deficit / hyperactivity disorder	Kafka MP, Hennen, J., "Psychostimulant augmentation during treatment with selective serotonin reuptake inhibitors in men with paraphilias and paraphilia-related disorders: a case series," *J. Clin. Psychiatry*, 61(9):664-70 (**2000**)
Generalized anxiety disorder	Lexapro® package insert
Weight management / Obesity	Boyer WF, "Potential indications for the selective serotonin reuptake inhibitors," *Int. Clin. Psychopharmacol.* 6 Suppl. 5:5-12 (**1992**)
Premenstrual dysphoric disorder	*Id.*
Anorexia nervosa	*Id.*
Bulimia nervosa	Prozac® package insert
Vasomotor flushing	Stearns V., *et al.*, "Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial," *JAMA*, 289(21):2827-34 (**2003**); Loprinzi, CL, *et al.*, "Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial," *Lancet*, 356(9247):2059-63 (**2000**)
Sexual dysfunction	McMahon CG and Touma K, "Treatment of premature ejaculation with paroxetine hydrochloride," *Int. J. Impot. Res.*, 11(5):241-245; discussion 246 (**1999**); Atmaca M, *et al.*, "The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study," *Int. J. Impot. Res.*, 14(6):502-5 (**2002**)

The following references also included to support the proposition that it is accepted in the art that reduction of negative feedback and augmentation of the serotonin reuptake mechanism can be effected by coadministration of SSRIs and $5HT_{1A}$ antagonists:

- Perez V, *et al.*, "Randomized, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment" *The Lancet*, 349:1594-97 (**1997**) (cited in IDS mailed January 27, 2004, as considered by Examiner February 7, 2005).

- Perez V, *et al.*, "Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors," *J. Clin. Psychopharmacol.* (**2001**) 21(1):36-45

RELATED PROCEEDINGS APPENDIX

No related appeals or interferences are pending.

J Clin Psychiatry. 1995 Nov;56(11):502-5.

Sertraline treatment of comorbid posttraumatic stress disorder and alcohol dependence.

Brady KT, Sonne SC, Roberts JM.

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston 29425, USA.

BACKGROUND: Posttraumatic stress disorder (PTSD) often co-occurs with alcohol dependence, yet little is known about treatment of this comorbidity. The serotonin selective reuptake inhibitors have been shown preliminarily to be effective in decreasing symptoms of PTSD but have not been studied in individuals with comorbid alcohol dependence. This is of particular interest as the SSRIs also have a modest effect in decreasing alcohol consumption. METHOD: In this preliminary trial, nine subjects with comorbid PTSD and alcohol dependence were treated in an open-label trial with sertraline for a 12-week period. Symptoms of PTSD and depression were monitored monthly with the Impact of Event Scale and the Hamilton Rating Scale for Depression (HAM-D). Alcohol consumption was monitored by a self-report instrument (Time-Line Follow-Back). RESULTS: There were significant decreases in all three symptom clusters of PTSD measured by overall PTSD symptom scores ($p < or = .001$) and in HAM-D scores ($p < or = .001$) during the follow-up period. Days of abstinence increased and average number of drinks decreased during the follow-up period. Four subjects claimed total abstinence during the follow-up period. CONCLUSION: While limited by small sample size and the open-label, nonblinded study design, this study suggests that sertraline may be useful in the treatment of PTSD complicated by alcoholism. The medication was well tolerated and subjects showed improvement in PTSD symptoms as well as decreased alcohol consumption. A controlled trial of sertraline in this population would be of interest.

Publication Types:

- Clinical Trial

PMID: 7592501 [PubMed - indexed for MEDLINE]

Int Clin Psychopharmacol. 1996 Jun;11(2):109-17.

Effects of fluoxetine at antidepressant doses on short-term outcome of detoxified alcoholics.

Janiri L, Gobbi G, Mannelli P, Pozzi G, Serretti A, Tempesta E.

Department of Psychiatry, Catholic University of Sacred Heart, Rome, Italy.

Compulsivity in alcohol-dependent patients is a frequent cause of early relapse in the post-detoxification period. The present study is a 2-month trial on detoxified alcoholics undergoing a double-blind placebo-controlled treatment with fluoxetine (20 mg/day). The rating instruments were the Hamilton Depression and Anxiety Scales, a visual analogue scale for alcohol craving and an original scale for evaluating alcohol withdrawal. The abstinence rate for fluoxetine-treated patients was significantly higher than in the placebo group, whereas no difference between treatments was found on the rating scales. Medical problems, additional psychiatric diagnoses, and family alcoholism were negatively correlated with abstinence. Two subgroups of patients having significantly different characteristics were identified as to the outcome, by means of cluster analysis. They are likely to represent two different stages in the evolution of alcoholism. Our results show that, independently from craving, fluoxetine at antidepressant doses is able to prevent relapses in weaned alcoholics. The anticompulsive therapy can positively influence the short-term outcome, while other factors are negatively associated with abstinence.

Publication Types:

- Clinical Trial
- Controlled Clinical Trial

PMID: 8803648 [PubMed - indexed for MEDLINE]

J Clin Psychiatry. 2000 Sep;61(9):664-70.

Psychostimulant augmentation during treatment with selective serotonin reuptake inhibitors in men with paraphilias and paraphilia-related disorders: a case series.

Kafka MP, Hennen J.

Department of Psychiatry, Harvard Medical School, Boston, USA. mpkafka@aol.com

BACKGROUND: We describe an open trial of psychostimulants (primarily methylphenidate sustained release [SR]) added to selective serotonin reuptake inhibitors (SSRIs; primarily fluoxetine) during the course of pharmacologic treatment of men with paraphilias and paraphilia-related disorders (PRDs). METHOD: Twenty-six men with paraphilias (N = 14) or PRDs (N = 12) were assessed for life-time mood disorders and attention-deficit/hyperactivity disorder (ADHD) as defined by DSM-IV. All men were assessed at baseline for total sexual outlet and average time per day associated with paraphilia/PRD sexual behaviors. The indications for the addition of a psychostimulant to a stable dose of SSRI included the retrospective diagnosis of ADHD with persistent adult symptoms despite pharmacotherapy with an SSRI (N = 17); residual paraphilia/PRD fantasies, urges, and activities despite SSRI pharmacotherapy (N = 16); the persistence or presence of residual depressive symptoms despite SSRI pharmacotherapy (N = 6); relapse or loss of SSRI efficacy during the treatment of sexual impulsivity disorders (N = 4); and treatment of SSRI-induced side effects (N = 4). RESULTS: SSRI pharmacotherapy (mean +/- SD duration = 8.8+/-11.1 months) had statistically significant effects in diminishing paraphilia/PRD-related total sexual outlet ($p < .001$) and average time/day spent in paraphilia/PRD sexual behavior ($p < .001$). Addition of methylphenidate SR (mean dose = 40 mg/day; mean +/- SD duration = 9.6+/-8.2 months) was associated with additional statistically significant effects on paraphilia/PRD-related total sexual outlet ($p = .003$) and average time per day ($p = .04$) in addition to improvement of putative residual ADHD and depressive symptoms. CONCLUSION: Methylphenidate SR can be cautiously and effectively combined with SSRI antidepressants to ameliorate paraphilias and paraphilia-related disorders for the indications listed above.

Publication Types:

- Case Reports
- Clinical Trial

MeSH Terms:

- Adult
- Ambulatory Care
- Attention Deficit Disorder with Hyperactivity/diagnosis

- Attention Deficit Disorder with Hyperactivity/drug therapy
- Attention Deficit Disorder with Hyperactivity/epidemiology
- Central Nervous System Stimulants/therapeutic use*
- Comorbidity
- Dose-Response Relationship, Drug
- Drug Administration Schedule
- Drug Therapy, Combination
- Human
- Male
- Mental Disorders/epidemiology
- Mental Disorders/psychology
- Methylphenidate/therapeutic use
- Middle Aged
- Paraphilias/drug therapy*
- Paraphilias/epidemiology
- Paraphilias/psychology
- Recurrence/prevention & control
- Serotonin Uptake Inhibitors/therapeutic use*
- Sexual Behavior/drug effects
- Sexual Behavior/psychology
- Treatment Outcome

Substances:

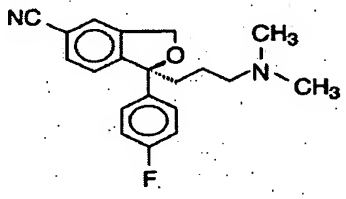
- Central Nervous System Stimulants
- Serotonin Uptake Inhibitors
- Methylphenidate

PMID: 11030487 [PubMed - indexed for MEDLINE]

LEXAPRO®
(escitalopram oxalate)
TABLETS/ORAL SOLUTION
Rx Only

DESCRIPTION

LEXAPRO® (escitalopram oxalate) is an orally administered selective serotonin reuptake inhibitor (SSRI). Escitalopram is the pure S-enantiomer (single isomer) of the racemic bicyclic phthalane derivative citalopram. Escitalopram oxalate is designated S-(+)-1-[3-(dimethyl-amino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate with the following structural formula:



$\cdot C_2H_2O_4$

The molecular formula is $C_{20}H_{21}FN_2O \cdot C_2H_2O_4$ and the molecular weight is 414.40.
Escitalopram oxalate occurs as a fine, white to slightly-yellow powder and is freely soluble in methanol and dimethyl sulfoxide (DMSO), soluble in isotonic saline solution, sparingly soluble in water and ethanol, slightly soluble in ethyl acetate, and insoluble in heptane.
LEXAPRO (escitalopram oxalate) is available as tablets or as an oral solution.
LEXAPRO tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 5 mg, 10 mg, and 20 mg escitalopram base. The 10 and 20 mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.
LEXAPRO oral solution contains escitalopram oxalate equivalent to 1 mg/mL escitalopram base. It also contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methylparaben, propylparaben, and natural peppermint flavor.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The mechanism of antidepressant action of escitalopram, the S-enantiomer of racemic citalopram, is presumed to be linked to potentiation of serotonergic activity in the central nervous system (CNS) resulting from its inhibition of CNS neuronal reuptake of serotonin (5-HT). *In vitro* and *in vivo* studies in animals suggest that escitalopram is a highly selective serotonin reuptake inhibitor (SSRI) with minimal effects on norepinephrine and dopamine neuronal reuptake. Escitalopram is at least 100-fold more potent than the R-enantiomer with respect to inhibition of 5-HT reuptake and inhibition of 5-HT neuronal firing rate. Tolerance to a model of antidepressant effect in rats was not induced by long-term (up to 5 weeks) treatment with escitalopram. Escitalopram has no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. Escitalopram also does not bind to, or has low affinity for, various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels. Antagonism of muscarinic, histaminergic, and adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular side effects of other psychotropic drugs.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of escitalopram are linear and dose-proportional in a dose range of 10 to 30 mg/day. Biotransformation of escitalopram is mainly hepatic, with a mean terminal half-life of about 27-32 hours. With once-daily dosing, steady state plasma concentrations are achieved within approximately one week. At steady state, the extent of accumulation of escitalopram in plasma in young healthy subjects was 2.2-2.5 times the plasma concentrations observed after a single dose. The tablet and the oral solution dosage forms of escitalopram oxalate are bioequivalent.

<u>Absorption and Distribution</u>

Following a single oral dose (20 mg tablet or solution) of escitalopram, peak blood levels occur at about 5 hours. Absorption of escitalopram is not affected by food.
The absolute bioavailability of citalopram is about 80% relative to an intravenous dose, and the volume of distribution of citalopram is about 12 L/kg. Data specific on escitalopram are unavailable.
The binding of escitalopram to human plasma proteins is approximately 56%.

Metabolism and Elimination

Following oral administrations of escitalopram, the fraction of drug recovered in the urine as escitalopram and S-demethylcitalopram (S-DCT) is about 8% and 10%, respectively. The oral clearance of escitalopram is 600 mL/min, with approximately 7% of that due to renal clearance.
Escitalopram is metabolized to S-DCT and S-didemethylcitalopram (S-DDCT). In humans, unchanged escitalopram is the predominant compound in plasma. At steady state, the concentration of the escitalopram metabolite S-DCT in plasma is approximately one-third that of escitalopram. The level of S-DDCT was not detectable in most subjects. *In vitro* studies show that escitalopram is at least 7 and 27 times more potent than S-DCT and S-DDCT, respectively, in the inhibition of serotonin reuptake, suggesting that the metabolites of escitalopram do not contribute significantly to the antidepressant actions of escitalopram. S-DCT and S-DDCT also have no or very low affinity for serotonergic ($5\text{-}HT_{1\text{-}7}$) or other receptors including alpha- and beta-adrenergic, dopamine ($D_{1\text{-}5}$), histamine ($H_{1\text{-}3}$), muscarinic ($M_{1\text{-}5}$), and benzodiazepine receptors. S-DCT and S-DDCT also do not bind to various ion channels including Na^+, K^+, Cl^-, and Ca^{++} channels.
In vitro studies using human liver microsomes indicated that CYP3A4 and CYP2C19 are the primary isozymes involved in the N-demethylation of escitalopram.

Population Subgroups

Age - Escitalopram pharmacokinetics in subjects ≥ 65 years of age were compared to younger subjects in a single-dose and a multiple-dose study. Escitalopram AUC and half-life were increased by approximately 50% in elderly subjects, and C_{max} was unchanged. 10 mg is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION**).
Gender - In a multiple-dose study of escitalopram (10 mg/day for 3 weeks) in 18 male (9 elderly and 9 young) and 18 female (9 elderly and 9 young) subjects, there were no differences in AUC, C_{max}, and half-life between the male and female subjects. No adjustment of dosage on the basis of gender is needed.
Reduced hepatic function - Citalopram oral clearance was reduced by 37% and half-life was doubled in patients with reduced hepatic function compared to normal subjects. 10 mg is the recommended dose of escitalopram for most hepatically impaired patients (see **DOSAGE AND ADMINISTRATION**).
Reduced renal function - In patients with mild to moderate renal function impairment, oral clearance of citalopram was reduced by 17% compared to normal subjects. No adjustment of dosage for such patients is recommended. No information is available about the pharmacokinetics of escitalopram in patients with severely reduced renal function (creatinine clearance < 20 mL/min).

Drug-Drug Interactions

In vitro enzyme inhibition data did not reveal an inhibitory effect of escitalopram on CYP3A4, -1A2, -2C9, -2C19, and -2E1. Based on *in vitro* data, escitalopram would be expected to have little inhibitory effect on *in vivo* metabolism mediated by these cytochromes. While *in vivo* data to address this question are limited, results from drug interaction studies suggest that escitalopram, at a dose of 20 mg, has no 3A4 inhibitory effect and a modest 2D6 inhibitory effect. See **Drug Interactions** under **PRECAUTIONS** for more detailed information on available drug interaction data.

Clinical Efficacy Trials

Major Depressive Disorder

The efficacy of LEXAPRO as a treatment for major depressive disorder was established in three, 8-week, placebo-controlled studies conducted in outpatients between 18 and 65 years of age who met DSM-IV criteria for major depressive disorder. The primary outcome in all three studies was change from baseline to endpoint in the Montgomery Asberg Depression Rating Scale (MADRS).
A fixed-dose study compared 10 mg/day LEXAPRO and 20 mg/day LEXAPRO to placebo and 40 mg/day citalopram. The 10 mg/day and 20 mg/day LEXAPRO treatment groups showed significantly greater mean improvement compared to placebo on the MADRS. The 10 mg and 20 mg LEXAPRO groups were similar on this outcome measure.
In a second fixed-dose study of 10 mg/day LEXAPRO and placebo, the 10 mg/day LEXAPRO treatment group showed significantly greater mean improvement compared to placebo on the MADRS.
In a flexible-dose study, comparing LEXAPRO, titrated between 10 and 20 mg/day, to placebo and citalopram,

titrated between 20 and 40 mg/day, the LEXAPRO treatment group showed significantly greater mean improvement compared to placebo on the MADRS.
Analyses of the relationship between treatment outcome and age, gender, and race did not suggest any differential responsiveness on the basis of these patient characteristics.
In a longer-term trial, 274 patients meeting (DSM-IV) criteria for major depressive disorder, who had responded during an initial 8-week, open-label treatment phase with LEXAPRO 10 or 20 mg/day, were randomized to continuation of LEXAPRO at their same dose, or to placebo, for up to 36 weeks of observation for relapse. Response during the open-label phase was defined by having a decrease of the MADRS total score to ≤ 12. Relapse during the double-blind phase was defined as an increase of the MADRS total score to ≥ 22, or discontinuation due to insufficient clinical response. Patients receiving continued LEXAPRO experienced a significantly longer time to relapse over the subsequent 36 weeks compared to those receiving placebo.

Generalized Anxiety Disorder

The efficacy of LEXAPRO in the treatment of Generalized Anxiety Disorder (GAD) was demonstrated in three, 8-week, multicenter, flexible-dose, placebo-controlled studies that compared LEXAPRO 10-20 mg/day to placebo in outpatients between 18 and 80 years of age who met DSM-IV criteria for GAD. In all three studies, LEXAPRO showed significantly greater mean improvement compared to placebo on the Hamilton Anxiety Scale (HAM-A).
There were too few patients in differing ethnic and age groups to adequately assess whether or not LEXAPRO has differential effects in these groups. There was no difference in response to LEXAPRO between men and women.

INDICATIONS AND USAGE

Major Depressive Disorder

LEXAPRO (escitalopram) is indicated for the treatment of major depressive disorder.
The efficacy of LEXAPRO in the treatment of major depressive disorder was established in three, 8-week, placebo-controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-IV category of major depressive disorder (see **CLINICAL PHARMACOLOGY**).
A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.
The efficacy of LEXAPRO in hospitalized patients with major depressive disorders has not been adequately studied.
The efficacy of LEXAPRO in maintaining a response, in patients with major depressive disorder who responded during an 8-week, acute-treatment phase while taking LEXAPRO and were then observed for relapse during a period of up to 36 weeks, was demonstrated in a placebo-controlled trial (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). Nevertheless, the physician who elects to use LEXAPRO for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

Generalized Anxiety Disorder

LEXAPRO is indicated for the treatment of Generalized Anxiety Disorder (GAD).
The efficacy of LEXAPRO was established in three, 8-week, placebo-controlled trials in patients with GAD (see **CLINICAL PHARMACOLOGY**).
Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.
The efficacy of LEXAPRO in the long-term treatment of GAD, that is, for more than 8 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use LEXAPRO for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **WARNINGS**).
Concomitant use in patients taking pimozide is contraindicated (see **Drug Interactions** – Pimozide and

Celexa).

LEXAPRO is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in LEXAPRO.

WARNINGS

Potential for Interaction with Monoamine Oxidase Inhibitors

In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that LEXAPRO should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping LEXAPRO before starting an MAOI.

Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

Clinical Worsening and Suicide Risk

Patients with major depressive disorder, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Nevertheless, patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms.

Because of the possibility of co-morbidity between major depressive disorder and other psychiatric and nonpsychiatric disorders, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with other psychiatric and nonpsychiatric disorders.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health-care providers. Prescriptions for LEXAPRO should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is

feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION, Discontinuation of Treatment with LEXAPRO**, for a description of the risks of discontinuation of LEXAPRO).
It should be noted that LEXAPRO is not approved for use in treating any indications in the pediatric population.

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that LEXAPRO is not approved for use in treating bipolar depression.

PRECAUTIONS

General

Discontinuation of Treatment with LEXAPRO

During marketing of LEXAPRO and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms.
Patients should be monitored for these symptoms when discontinuing treatment with LEXAPRO. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see **DOSAGE AND ADMINISTRATION**).

Abnormal Bleeding

Published case reports have documented the occurrence of bleeding episodes in patients treated with psychotropic drugs that interfere with serotonin reuptake. Subsequent epidemiological studies, both of the case-control and cohort design, have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. In two studies, concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) or aspirin potentiated the risk of bleeding (see **Drug Interactions**). Although these studies focused on upper gastrointestinal bleeding, there is reason to believe that bleeding at other sites may be similarly potentiated. Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of LEXAPRO with NSAIDs, aspirin, or other drugs that affect coagulation.

Hyponatremia

One case of hyponatremia has been reported in association with LEXAPRO treatment. Several cases of hyponatremia or SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with racemic citalopram. All patients with these events have recovered with discontinuation of escitalopram or citalopram and/or medical intervention. Hyponatremia and SIADH have also been reported in association with other marketed drugs effective in the treatment of major depressive disorder.

Activation of Mania/Hypomania

In placebo-controlled trials of LEXAPRO in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with LEXAPRO and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with LEXAPRO treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, LEXAPRO should be used cautiously in patients with a history of mania.

Seizures

Although anticonvulsant effects of racemic citalopram have been observed in animal studies, LEXAPRO has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical

studies during the product's premarketing testing. In clinical trials of LEXAPRO, cases of convulsion have been reported in association with LEXAPRO treatment. Like other drugs effective in the treatment of major depressive disorder, LEXAPRO should be introduced with care in patients with a history of seizure disorder.

Interference with Cognitive and Motor Performance

In a study in normal volunteers, LEXAPRO 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that LEXAPRO therapy does not affect their ability to engage in such activities.

Use in Patients with Concomitant Illness

Clinical experience with LEXAPRO in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using LEXAPRO in patients with diseases or conditions that produce altered metabolism or hemodynamic responses.

LEXAPRO has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of LEXAPRO in hepatically impaired patients is 10 mg/day (see **DOSAGE AND ADMINISTRATION**).

Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with LEXAPRO, however, it should be used with caution in such patients (see **DOSAGE AND ADMINISTRATION**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe LEXAPRO.

In a study in normal volunteers, LEXAPRO 10 mg/day did not impair psychomotor performance. The effect of LEXAPRO on psychomotor coordination, judgment, or thinking has not been systematically examined in controlled studies. Because psychoactive drugs may impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that LEXAPRO therapy does not affect their ability to engage in such activities.

Patients should be told that, although LEXAPRO has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of LEXAPRO and alcohol in depressed patients is not advised.

Patients should be made aware that escitalopram is the active isomer of Celexa (citalopram hydrobromide) and that the two medications should not be taken concomitantly.

Patients should be advised to inform their physician if they are taking, or plan to take, any prescription or over-the-counter drugs, as there is a potential for interactions.

Patients should be cautioned about the concomitant use of LEXAPRO and NSAIDs, aspirin, or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breastfeeding an infant.

While patients may notice improvement with LEXAPRO therapy in 1 to 4 weeks, they should be advised to continue therapy as directed.

Patients and their families should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia, hypomania, mania, worsening of depression, and suicidal ideation, especially early during antidepressant treatment. Such symptoms should be reported to the patient's physician, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Laboratory Tests

There are no specific laboratory tests recommended.

Concomitant Administration with Racemic Citalopram

Citalopram - Since escitalopram is the active isomer of racemic citalopram (Celexa), the two agents should not be

coadministered.

Drug Interactions
CNS Drugs - Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs.
Alcohol - Although LEXAPRO did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking LEXAPRO is not recommended.
Monoamine Oxidase Inhibitors (MAOIs) - See **CONTRAINDICATIONS** and **WARNINGS.**

Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin potentiated the risk of bleeding. Thus, patients should be cautioned about the use of such drugs concurrently with LEXAPRO.

Cimetidine - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown.
Digoxin - In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin.
Lithium - Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when LEXAPRO and lithium are coadministered.
Pimozide and Celexa - In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known.
Sumatriptan - There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised.
Theophylline - Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated.
Warfarin - Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown.
Carbamazepine - Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered.
Triazolam - Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam.
Ketoconazole - Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram.
Ritonavir - Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram.
CYP3A4 and -2C19 Inhibitors - *In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes

involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance.

Drugs Metabolized by Cytochrome P4502D6 - *In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6.

Metoprolol - Administration of 20 mg/day LEXAPRO for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of LEXAPRO and metoprolol had no clinically significant effects on blood pressure or heart rate.

Electroconvulsive Therapy (ECT) - There are no clinical studies of the combined use of ECT and escitalopram.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Racemic citalopram was administered in the diet to NMRI/BOM strain mice and COBS WI strain rats for 18 and 24 months, respectively. There was no evidence for carcinogenicity of racemic citalopram in mice receiving up to 240 mg/kg/day. There was an increased incidence of small intestine carcinoma in rats receiving 8 or 24 mg/kg/day racemic citalopram. A no-effect dose for this finding was not established. The relevance of these findings to humans is unknown.

Mutagenesis

Racemic citalopram was mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) in 2 of 5 bacterial strains (Salmonella TA98 and TA1537) in the absence of metabolic activation. It was clastogenic in the *in vitro* Chinese hamster lung cell assay for chromosomal aberrations in the presence and absence of metabolic activation. Racemic citalopram was not mutagenic in the *in vitro* mammalian forward gene mutation assay (HPRT) in mouse lymphoma cells or in a coupled *in vitro/in vivo* unscheduled DNA synthesis (UDS) assay in rat liver. It was not clastogenic in the *in vitro* chromosomal aberration assay in human lymphocytes or in two *in vivo* mouse micronucleus assays.

Impairment of Fertility

When racemic citalopram was administered orally to 16 male and 24 female rats prior to and throughout mating and gestation at doses of 32, 48, and 72 mg/kg/day, mating was decreased at all doses, and fertility was decreased at doses ≥ 32 mg/kg/day. Gestation duration was increased at 48 mg/kg/day.

Pregnancy

Pregnancy Category C

In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis).

When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis.

In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses.

In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit.
When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study.
There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy-Nonteratogenic Effects
Neonates exposed to LEXAPRO and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see **WARNINGS**).
When treating a pregnant woman with LEXAPRO during the third trimester, the physician should carefully consider the potential risks and benefits of treatment (see **DOSAGE AND ADMINISTRATION**).

Labor and Delivery
The effect of LEXAPRO on labor and delivery in humans is unknown.

Nursing Mothers
Racemic citalopram, like many other drugs, is excreted in human breast milk. There have been two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of citalopram by its mother and, in the second case, no follow-up information was available. The decision whether to continue or discontinue either nursing or LEXAPRO therapy should take into account the risks of citalopram exposure for the infant and the benefits of LEXAPRO treatment for the mother.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established (see **WARNINGS-Clinical Worsening and Suicide Risk**).

Geriatric Use
Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of LEXAPRO in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of LEXAPRO between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of LEXAPRO cannot be ruled out.
In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged (see **CLINICAL PHARMACOLOGY**). 10 mg/day is the recommended dose for elderly patients (see **DOSAGE AND ADMINISTRATION**).
Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

ADVERSE REACTIONS

Adverse event information for LEXAPRO was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for LEXAPRO in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Events Associated with Discontinuation of Treatment

Major Depressive Disorder

Among the 715 depressed patients who received LEXAPRO in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day LEXAPRO was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day LEXAPRO (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients).

Generalized Anxiety Disorder

Among the 429 GAD patients who received LEXAPRO 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with LEXAPRO, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%).

Incidence of Adverse Events in Placebo-Controlled Clinical Trials

Major Depressive Disorder

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received LEXAPRO at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients.

The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence (see **TABLE 1**).

TABLE 1
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials for
Major Depressive Disorder*

Body System / Adverse Event	(Percentage of Patients Reporting Event) LEXAPRO (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

*Events reported by at least 2% of patients treated with LEXAPRO are reported, except for the following events which had an incidence on placebo ≥ LEXAPRO: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety.

[1]Primarily ejaculatory delay.

[2]Denominator used was for males only (N=225 LEXAPRO; N=188 placebo).

[3]Denominator used was for females only (N=490 LEXAPRO; N=404 placebo).

Generalized Anxiety Disorder

Table 2 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received LEXAPRO 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with LEXAPRO and for which the incidence in patients treated with LEXAPRO was greater than the incidence in placebo-treated patients.

The most commonly observed adverse events in LEXAPRO patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 2**).

TABLE 2

Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder*

Body System / Adverse Event	(Percentage of Patients Reporting Event) LEXAPRO (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		

Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

*Events reported by at least 2% of patients treated with LEXAPRO are reported, except for the following events which had an incidence on placebo ≥ LEXAPRO: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis.

[1]Primarily ejaculatory delay.

[2]Denominator used was for males only (N=182 LEXAPRO; N=195 placebo).

[3]Denominator used was for females only (N=247 LEXAPRO; N=232 placebo).

Dose Dependency of Adverse Events

The potential dose dependency of common adverse events (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg LEXAPRO groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg LEXAPRO-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day LEXAPRO-treated patients was greater (86%). Table 3 shows common adverse events that occurred in the 20 mg/day LEXAPRO group with an incidence that was approximately twice that of the 10 mg/day LEXAPRO group and approximately twice that of the placebo group.

TABLE 3
Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo, 10 mg/day LEXAPRO, or 20 mg/day LEXAPRO

Adverse Event	Placebo (N=311)	10 mg/day LEXAPRO (N=310)	20 mg/day LEXAPRO (N=125)

Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

*Adverse events with an incidence rate of at least 5% in either of the LEXAPRO groups and with an incidence rate in the 20 mg/day LEXAPRO group that was approximately twice that of the 10 mg/day LEXAPRO group and the placebo group.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

Table 4 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials.

TABLE 4

Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	**LEXAPRO**	**Placebo**
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Vital Sign Changes

LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with LEXAPRO treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving LEXAPRO indicated that LEXAPRO treatment is not associated with orthostatic changes.

Weight Changes

Patients treated with LEXAPRO in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight.

Laboratory Changes
LEXAPRO and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with LEXAPRO treatment.

ECG Changes
Electrocardiograms from LEXAPRO (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for LEXAPRO and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for LEXAPRO and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither LEXAPRO nor racemic citalopram were associated with the development of clinically significant ECG abnormalities.

Other Events Observed During the Premarketing Evaluation of LEXAPRO
Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with LEXAPRO for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 1 & 2, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with LEXAPRO, they were not necessarily caused by it.
Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients.
Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein.
Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased.
Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult.
General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall.
Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical.
Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia.
Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness.
Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency.
Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses.
*% based on female subjects only: N= 905
Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis.
Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule.
Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste.
Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency,

kidney stone, dysuria, blood in urine.

Events Reported Subsequent to the Marketing of Racemic Citalopram and Escitalopram
Although no causal relationship to racemic citalopram or escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and with escitalopram treatment during postmarketing experience and were not observed during the premarketing evaluation of citalopram or escitalopram: acute renal failure, angioedema, toxic epidermal necrolysis, gastrointestinal hemorrhage, grand mal seizures (or convulsions), neuroleptic malignant syndrome, pancreatitis, QT prolongation, rhabdomyolysis, serotonin syndrome, thrombocytopenia, torsades de pointes.

Events Reported Subsequent to the Marketing of Racemic Citalopram (not observed during the postmarketing experience with escitalopram)
Although no causal relationship to racemic citalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with racemic citalopram treatment and were not observed during the premarketing evaluation of citalopram: akathisia, allergic reaction, anaphylaxis, choreoathetosis, delirium, dyskinesia, ecchymosis, erythema multiforme, hemolytic anemia, hepatic necrosis, myoclonus, nystagmus, priapism, prolactinemia, prothrombin decreased, spontaneous abortion, thrombosis, and ventricular arrhythmia.

Events Reported Subsequent to the Marketing of Escitalopram (not observed during the postmarketing experience with citalopram)
Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment and were not observed during the premarketing evaluation of escitalopram: aggression, atrial fibrillation, seizures, diplopia, dystonia, extrapyramidal disorders, abnormal gait, visual hallucinations, hepatitis, hypotension, myocardial infarction, orthostatic hypotension, pulmonary embolism, SIADH, ventricular tachycardia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class
LEXAPRO is not a controlled substance.

Physical and Psychological Dependence
Animal studies suggest that the abuse liability of racemic citalopram is low. LEXAPRO has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with LEXAPRO did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate LEXAPRO patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience
There have been reports of LEXAPRO overdose involving doses of up to 600 mg. All patients recovered and no symptoms associated with the overdoses were reported. In clinical trials of racemic citalopram, there were no reports of fatal citalopram overdose involving overdoses of up to 2000 mg. During the postmarketing evaluation of citalopram, like other SSRIs, a fatal outcome in a patient who has taken an overdose of citalopram has been rarely reported.
Postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as non-fatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, sinus tachycardia, and convulsions. In more rare cases, observed symptoms included amnesia, confusion, coma, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of torsades de pointes).

Management of Overdose
Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for LEXAPRO.
In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Major Depressive Disorder
Initial Treatment
The recommended dose of LEXAPRO is 10 mg once daily. A fixed-dose trial of LEXAPRO demonstrated the effectiveness of both 10 mg and 20 mg of LEXAPRO, but failed to demonstrate a greater benefit of 20 mg over 10 mg (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). If the dose is increased to 20 mg, this should occur after a minimum of one week.
LEXAPRO should be administered once daily, in the morning or evening, with or without food.
Special Populations
10 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment.
No dosage adjustment is necessary for patients with mild or moderate renal impairment. LEXAPRO should be used with caution in patients with severe renal impairment.

Treatment of Pregnant Women During the Third Trimester
Neonates exposed to LEXAPRO and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with LEXAPRO during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering LEXAPRO in the third trimester.

Maintenance Treatment
It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacological therapy beyond response to the acute episode. Systematic evaluation of continuing LEXAPRO 10 or 20 mg/day for periods of up to 36 weeks in patients with major depressive disorder who responded while taking LEXAPRO during an 8-week, acute-treatment phase demonstrated a benefit of such maintenance treatment (see **Clinical Efficacy Trials** under **CLINICAL PHARMACOLOGY**). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Generalized Anxiety Disorder
Initial Treatment
The recommended starting dose of LEXAPRO is 10 mg once daily. If the dose is increased to 20 mg, this should occur after a minimum of one week.
LEXAPRO should be administered once daily, in the morning or evening, with or without food.

Maintenance Treatment
Generalized anxiety disorder is recognized as a chronic condition. The efficacy of LEXAPRO in the treatment of GAD beyond 8 weeks has not been systematically studied. The physician who elects to use LEXAPRO for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

Discontinuation of Treatment with LEXAPRO
Symptoms associated with discontinuation of LEXAPRO and other SSRIs and SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more

gradual rate.

Switching Patients To or From a Monoamine Oxidase Inhibitor
At least 14 days should elapse between discontinuation of an MAOI and initiation of LEXAPRO therapy. Similarly, at least 14 days should be allowed after stopping LEXAPRO before starting an MAOI (see **CONTRAINDICATIONS** and **WARNINGS**).

HOW SUPPLIED
5 mg Tablets:
Bottle of 100 NDC # 0456-2005-01
White to off-white, round, non-scored, film-coated. Imprint "FL" on one side of the tablet and "5" on the other side.
10 mg Tablets:
Bottle of 100 NDC # 0456-2010-01
10 x 10 Unit Dose NDC # 0456-2010-63
White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "10".
20 mg Tablets:
Bottle of 100 NDC # 0456-2020-01
10 x 10 Unit Dose NDC # 0456-2020-63
White to off-white, round, scored, film-coated. Imprint on scored side with "F" on the left side and "L" on the right side.
Imprint on the non-scored side with "20".
Oral Solution:
5 mg/5 mL, peppermint flavor (240 mL) NDC # 0456-2101-08
Store at 25°C (77°F); excursions permitted to 15 - 30°C (59-86°F).

ANIMAL TOXICOLOGY
Retinal Changes in Rats
Pathologic changes (degeneration/atrophy) were observed in the retinas of albino rats in the 2-year carcinogenicity study with racemic citalopram. There was an increase in both incidence and severity of retinal pathology in both male and female rats receiving 80 mg/kg/day. Similar findings were not present in rats receiving 24 mg/kg/day of racemic citalopram for two years, in mice receiving up to 240 mg/kg/day of racemic citalopram for 18 months, or in dogs receiving up to 20 mg/kg/day of racemic citalopram for one year.
Additional studies to investigate the mechanism for this pathology have not been performed, and the potential significance of this effect in humans has not been established.

Cardiovascular Changes in Dogs
In a one-year toxicology study, 5 of 10 beagle dogs receiving oral racemic citalopram doses of 8 mg/kg/day died suddenly between weeks 17 and 31 following initiation of treatment. Sudden deaths were not observed in rats at doses of racemic citalopram up to 120 mg/kg/day, which produced plasma levels of citalopram and its metabolites demethylcitalopram and didemethylcitalopram (DDCT) similar to those observed in dogs at 8 mg/kg/day. A subsequent intravenous dosing study demonstrated that in beagle dogs, racemic DDCT caused QT prolongation, a known risk factor for the observed outcome in dogs.

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Rev. 08/04

Introduction

The development in psychopharmacological treatment has placed serotonin as an important neurotransmitter in various psychiatric disorders. The 5-HT reuptake inhibitors seem to be effective in a range of different syndromes such as melancholia, major depression, atypical depression, dysphoria, recurrent brief depression, panic disorder, obsessive compulsive disorders, kleptomania, dementia, pain and alcoholism.

Due to this wide range of syndromes in which effect is reported, it has been suggested, that 5-HT uptake inhibitors should be named emotional stabilizers rather than antidepressants. It is a question whether serotonin plays a specific role in these syndromes, or the 5-HT uptake inhibitors influence a pathway common for all above mentioned syndromes. Maybe we are not even close to finding the central pathogenic mechanism for psychiatric disorders. By means of the selective substances available today, we have a method which leads us to a better understanding of the biology underlying the syndromes. The important issue is, however, that the selective drugs, i.e. 5-HT uptake inhibitors, are clinically effective and of benefit to the patients.

Citalopram is a 5-HT uptake inhibitor, the most selective marketed today. Citalopram has an excellent pharmacokinetic profile, a half-life of about 36 h and a minimal risk of interaction. Further to this, citalopram has only few, mild and transient side effects and is therefore well accepted generally, and also by groups who are sensitive to adverse effects. Citalopram is proven to be effective in depressive patients and excellent results are reported when treating elderly depressed patients with and without senile dementia. Patients suffering from panic disorder have also been treated with good results and high tolerability.

This publication contains proceedings from a symposium held in Florence, Italy, 11 June 1991 at the 5th World Congress of Biological Psychiatry and two further papers. A review of diagnoses in which 5-HT uptake inhibitors are reported effective is given. Serotonin in panic disorder is dealt with in detail. The difference in pharmacokinetic profile between 5-HT uptake inhibitors is reviewed with emphasis on citalopram. The clinical effect of citalopram in depression is illustrated by means of a meta-analysis, and the effect of citalopram in elderly patients is also presented. A view into the future treatment of depression was given as an introduction to the last part of the programme.

In addition, some recent placebo controlled short-term data for citalopram and preliminary evidence on the citalopram efficacy in relapse prevention is also described.

As chairman of the symposium, I express my sincere thanks to the speakers and authors for their contributions.

Rasmus Fog

Potential Indications for the Selective Serotonin Reuptake Inhibitors

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The selective serotonin reuptake inhibitors (SSRIs) include fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. These medications may be effective for a variety of indications. The literature clearly supports their efficacy in some of these conditions in major depression. Data concerning their use in other areas is clearly preliminary but promising. These include reports of treatment of obsessive–compulsive disorder, atypical depression, panic disorder, premenstrual tension, eating disorders, substance use disorders, chronic pain, dementia, and personality disorders with aggressive or impulsive features. The variety of clinical uses for the SSRIs may compel re-examination of traditional diagnostic categories and theories of how antidepressants work.

Introduction

The selective serotonin reuptake inhibitors (SSRIs) are an important new class of medications in clinical psychiatry. The class includes fluoxetine, fluvoxamine, citalopram, paroxetine and sertraline. There is a large body of literature supporting their efficacy in major depression (Boyer and Feighner, 1991). As these compounds come into extensive use reports are emerging of their possible efficacy in a wider range of disorders. This review will briefly note some of these areas. The intent will not be to argue that the SSRIs are effective for all of these indications. The lack of controlled data clearly does not allow such a conclusion. Instead the aim will be to alert the reader to areas that bear watching and to consider the implications of these findings.

Obsessive–compulsive disorder (OCD)

A number of double-blind studies of sertraline and fluvoxamine in obsessive–compulsive disorder have been reported. With the exception of one small study (Jenike *et al.*, 1990*a*) these have shown clinically and statistically significant effects in OCD (Perse *et al.*, 1987; Bick *et al.*, 1989; Goodman, *et al.*, 1989; Chouinard *et al.*, 1990; Jenike *et al.*, 1990*b*). One study found fluvoxamine to be significantly superior to desipramine, a relatively more potent noradrenergic uptake inhibitor (Goodman *et al.*, 1990). Fluoxetine has also been studied in a number of open trials with encouraging results (Fontaine *et al.*, 1985; Turner *et al.*, 1985; Jenike *et al.*, 1989; Levine *et al.*, 1989*a*, *b*; Liebowitz *et al.*, 1990; Riddle *et al.*, 1990).

A number of disorders which share features with OCD may also respond to SSRIs. Fallon and colleagues treated seven patients with excessive religious scrupulosity for at

least 8 weeks with fluoxetine or clomipramine. At the end of the trial 5/7 were much improved. These results suggest that extreme moral or religious concerns may be a form of OCD and may be treatable with serotonin reuptake blockers (Fallon *et al.*, 1990). Benarroche reported an 80% response rate of trichotillomania to fluoxetine. All patients relapsed after medication was withdrawn (Parker, 1982). Viswanathan described a patient who experienced severe, recurrent, intrusive, but ego-syntonic fears that she or someone in her family had cancer. This was successfully relieved in two separate trials of fluoxetine, 20 mg b.i.d., but not by desipramine or buspirone (Viswanathan *et al.*, 1991).

Atypical depression

Atypical depression is an important, if imprecisely defined, clinical concept. Some evidence suggests that monoamine oxidase inhibitors (MAOIs) are superior to tricyclic antidepressants for these patients. However use of the MAOIs is limited by the need for dietary restrictions and concern for drug interactions. Pande *et al.* randomly assigned 27 patients with atypical depression as defined by Quitkin *et al.* to 6 weeks of double-blind treatment with fluoxetine 20–60 mg daily or phenelzine, 45–90 mg daily. The results showed 92% response with fluoxetine and 67% with phenelzine. Phenelzine patients also had significantly more side effects. More patients elected to stay on fluoxetine than phenelzine at the end of the trial (Pande *et al.*, 1991).

Panic disorder

Humble and colleagues treated 20 panic disorder patients with citalopram, up to 60 mg/day, in an 8 week open study. Citalopram appeared effective and well-tolerated (Humble *et al.*, 1989). Similar positive effects were reported in two open trials of fluoxetine (Gorman *et al.*, 1987; Schneier *et al.*, 1990). One controlled study has compared fluvoxamine with maprotiline, a noradrenaline uptake inhibitor, in panic disorder. Fluvoxamine was significantly effective but maprotiline was not (Den-Boer and Westenberg, 1988).

Premenstrual tension (PMS)

Two double-blind placebo-controlled studies have shown fluoxetine to significantly decrease the affective symptoms accompanying PMS (Rickels *et al.*, 1990; Stone *et al.*, 1990). However a study with fluvoxamine failed to show significant differences from placebo (Veeninga *et al.*, 1990). This may have been due to the strong placebo effect in this study or it may suggest that all SSRIs are not equally effective in this condition.

Personality disorders

Markovitz and associates treated 22 patients with borderline or schizotypal personality disorders in an open, 12-week trial of fluoxetine. All had initially sought help for anxiety or depression and 13 met criteria for major depression. There were significant reductions in self-injury and in scores on the Hopkins symptom checklist in patients with either or both diagnoses (Markovitz, *et al.*, 1991). Two open studies of fluoxetine have also reported significant improvement in patients with severe borderline personality disorder (Cornelius *et al.*, 1990; Norden, 1991). There are however no controlled studies.

Substance abuse

Naranjo and colleagues tested citalopram in 39 non-depressed males who were early problem drinkers. Citalopram, 20 mg/day, did not show an effect but 40 mg/day decreased the number of drinks consumed and increased the number of abstinent days (Naranjo *et al.*, 1987). These same investigators found similar results with other serotonin reuptake blockers (Naranjo and Sellers, 1989).

Some evidence suggests that fluoxetine may antagonize the reinforcing properties of cocaine (Richardson and Roberts, 1991). Pollack and Rosenbaum gave fluoxetine to 11 cocaine-abusing heroin addicts in a methadone maintenance program. Of the eight patients who completed the trial, five were successfully treated for cocaine use. They concluded that fluoxetine may be a useful addition in the treatment of cocaine abuse (Pollack and Rosenbaum, 1991).

Eating disorders

Weight loss is a common side effect of the SSRIs. Several studies have suggested that fluoxetine or sertraline may be a useful adjunct in the treatment of obesity in non-depressed patients. Fortunately, the degree of weight loss appears to be proportional to the degree of initial obesity (Levine et al., 1987; Orzack *et al.*, 1990), so that weight loss in normal or underweight individuals is rarely a problem.

Clark and Rosenblatt studied 80 obese diabetic patients. Sertraline (150 mg/day) was associated with significantly more weight loss than placebo (2.9 vs. 0.76 kg) (Clark and Rosenblatt, 1989). Similarly, Feighner and Rosenblatt reported significantly more weight loss with sertraline, 50–200 mg/day, than placebo in 150 non-depressed obese outpatients (Feighner and Rosenblatt, 1989).

Weight loss with fluoxetine is associated with higher doses than usually used for depression, in the range of 40–60 mg/day (Levine, *et al.*, 1989*a*). Ferguson and Feighner found that fluoxetine (average 65 mg/day) produced significantly more weight loss than placebo among 150 non-depressed obese outpatients. Fluoxetine was also associated with a trend for more weight loss than benzphetamine (Ferguson and Feighner, 1987). Marcus and colleagues reported that patients treated with 60 mg/day of fluoxetine in addition to behavior therapy lost more weight than those treated with behavior therapy plus placebo (Marcus *et al.*, 1990).

Maintenance of weight loss is a problem with the SSRIs, as it is with other weight-loss strategies. Darga and co-workers compared diet plus either fluoxetine or placebo in the treatment of 45 non-depressed obese patients. The fluoxetine-treated patients lost significantly more weight, but had a tendency to regain it. At the end of 1 year there were no significant differences between the fluoxetine and placebo groups (Darga *et al.*, 1991).

The SSRIs may have beneficial effects in other eating disorders. Enas and colleagues compared two doses of fluoxetine in 382 outpatient bulimic women. At 60 mg/day fluoxetine was significantly superior to placebo. Fluoxetine 20 mg/day had an intermediate

effect (Enas *et al.*, 1989). This dose-response effect is similar to that noted above for weight loss with fluoxetine.

Weltzin and colleagues reported on 31 patients with chronic anorexia nervosa who were treated with fluoxetine for an average of 11 months. During the study 29 patients (94%) maintained their body weight at or above 85% average body weight for height. Global Response was judged to be good in 10, partial in 17 and poor in 6. Paradoxically, patients who were partial or poor responders were significantly more depressed at baseline than good responders (Weltzin *et al.*, 1991). This suggests that fluoxetine's effect may have been independent of its antidepressant activity. Gwirtsman and associates reported that six patients with chronic anorexia nervosa showed improved mood and weight gain with fluoxetine (Gwirtsman *et al.*, 1990). Ferguson reported successful use of fluoxetine in another patient with anorexia nervosa (Ferguson, 1987).

Other potential indications

Goldman and Janecek gave fluoxetine, 20 mg/day, to eight patients with schizophrenia in an open trial (Goldman and Janecek, 1990). Clinical state improved in all patients. Violent incidents decreased, while participation in programs and socialization increased. The addition of fluoxetine to neuroleptic medication has also been reported to be helpful in other patients with chronic schizophrenia (Goff *et al.*, 1990; Lindenmayer *et al.*, 1990).

Kafka reported that 9/10 men with DSM-III-R non-paraphilic sexual addiction or paraphilias had improved sexual behaviors while treated with fluoxetine, imipramine, or lithium (Kafka, 1991*a*). Kafka also reported that fluoxetine successfully treated a rapist with intrusive and persistent paraphilic rape fantasies. Symptoms of impulsiveness, anxiety and depression were also markedly improved (Kafka, 1991*b*). Another investigator reported the successful use of fluoxetine in treatment of a fetish (Lorefice, 1991).

Todd reported three cases of autism in which fluoxetine, 20 mg/day, was helpful in reducing behaviors such as stereotypies rituals, and violent outbursts (Todd, 1991). Ghaziuddin and colleagues presented four more cases of autism in which fluoxetine was helpful, especially in the presence of concomitant depression (Ghaziuddin *et al.*, 1991).

The SSRIs also improve some of the emotional and behavioral symptoms that accompany dementia (Nyth *et al.*, 1987, 1989; Martin *et al.*, 1989; Sobin *et al.*, 1989). Whether there is any primary improvement in memory function is unsettled.

Hanzel and associates compared fluoxetine with protriptyline in 12 patients with obstructive sleep apnea. Both drugs decreased periods of apnea and hypopneas, but fluoxetine was better tolerated (Hanzel *et al.*, 1991).

Pain is another area in which the SSRIs may be helpful. Theesen and March (1989) reported a patient with painful diabetic neuropathy and major depression, both of which responded to fluoxetine. Fluoxetine may also have some use in the treatment of headache (Diamond and Freitag, 1989) and fibrositis (Geller, 1989).

Discussion

An important theoretical question is how one class of medication could be helpful for such a disparate group of disorders. Part of this dilemma is artifactual: it is relatively common for patients with one disorder, for example borderline personality disorder, to present with features of other disorders. In this case the SSRI may be treating a feature of an associated disorder and contributing only indirectly to improvement in another.

Another hypothesis is one put forward by Van Praag and others; that abnormal serotonin function affects behavior in ways that cross traditional nosologic boundaries. For example, disturbed serotonin function may be related to depressed mood, anxiety, impulsivity, and aggression (Apter *et al.*, 1990). Many of the conditions for which the SSRIs are helpful have varying degrees of these features. The implication of this theory is that traditional nosologic boundaries may need to be re-examined in light of this biochemical and pharmacologic data.

A related possibility is that abnormalities in serotonin function may only begin a pathologic process, the ultimate form of which is shaped by the social environment, intrapsychic factors or other biological conditions. This is an interesting possibility as it is reminiscent of earlier psychodynamic formulations regarding symptom "choice".

Another hypothesis is that SSRIs may have a therapeutic effect which is unrelated to the etiology of the disorder. There are many examples of illnesses in which effective treatments do not act on the cause of the illness. Diuretics are helpful for hypertension although high blood pressure is rarely, if ever, caused by water or salt retention. Insulin is used in type II diabetes even though the pathology lies in sub-sensitivity to insulin rather than lack of insulin. Histamine-1 receptor blockers and antacids are mainstays of therapy for gastrointestinal ulcers although ulcers are not caused by an excess of histamine and only rarely by excessive acid production. These speculations on the apparently broad range of indications for the SSRIs are also of course not mutually exclusive. It will be very interesting to follow these areas to see which alternatives are supported.

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Clinical Pharmacokinetics of Citalopram and Other Selective Serotonergic Reuptake Inhibitors (SSRI)

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The pharmacokinetics and clinical properties of clomipramine, the classic 5-HT uptake inhibiting antidepressant is well known. Within the last years, several new and more selective serotonin uptake inhibitors have been introduced in clinical practice, including trazodone, citalopram, paroxetine, femoxetine, fluvoxamine and fluoxetine. They differ by their chemical structure, and therefore, important differences can be expected with respect to their metabolism and kinetics in man. In this presentation, the following points will be addressed: Present knowledge about their metabolism and their kinetics, taking into account that most of them are racemates, whose clinical role is only partially understood, including that of the metabolites. It will further be examined whether they are candidates for a genetic polymorphism of metabolism of the debrisoquine-spartein-dextromethorphan type. This may e.g. be suspected for fluoxetine which interferes strongly with the metabolism of tricyclic antidepressants. Finally, data of the literature will be analysed about a possible relationship between the clinical efficacy of these drugs and their plasma levels, including those of their active metabolites.

Introduction

The classical tricyclic antidepressants have many similarities in pharmacodynamics and pharmacokinetics, as a consequence of their common chemical structure. Nevertheless, they differ widely in potency and selectivity and inhibition of the reuptake of serotonin and norepinephrine (Table 1). Within the last few years, several more potent and more selective serotonin reuptake inhibitors (SSRI) have been introduced as antidepressants in clinical practice or are still under investigation (Feighner and Boyer, 1991). These include citalopram, femoxetine, fluoxetine, fluvoxamine, paroxetine and sertraline, not to forget the earlier introduced drug trazodone for its selectivity but low potency (Table 1).

The pharmacological profile—chemical structure relationship of SSRIs

Among the tricyclic antidepressant drugs, clomipramine is considered to be the most potent 5-HT reuptake inhibitor *in vitro*. However, due to the presence of its metabolite demethylclomipramine, a potent norepinephrine reuptake inhibitor, the plasma concentrations of which often exceed those of the parent compound, clomipramine loses *in vivo* much of its selectivity. Among the new SSRIs, paroxetine is the most potent, and citalopram the most selective serotonin reuptake inhibitor. Citalopram's main metabolite,

PV 3453 DPP

PROZAC®
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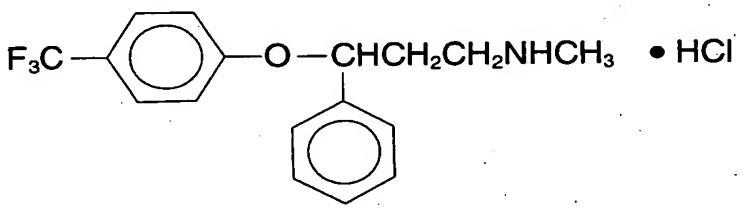
DESCRIPTION

Prozac® (fluoxetine hydrochloride) is a psychotropic drug for oral administration. It is also marketed for the treatment of premenstrual dysphoric disorder (Sarafem™, fluoxetine hydrochloride). It is designated (±)-N-methyl-3-phenyl-3-[(α,α,α-trifluoro-*p*-tolyl)oxy]propylamine hydrochloride and has the empirical formula of $C_{17}H_{18}F_3NO \bullet HCl$. Its molecular weight is 345.79. The structural formula is:



Fluoxetine hydrochloride is a white to off-white crystalline solid with a solubility of 14 mg/mL in water.

Each Pulvule® contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol), 20 mg (64.7 µmol), or 40 mg (129.3 µmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

Each tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 µmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10-mg tablet contains FD&C Blue No. 1 aluminum lake, and polysorbate 80.

The oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 µmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.

Prozac Weekly™ capsules, a delayed release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 µmol) of fluoxetine. The capsules also contain D&C Yellow No. 10, FD&C Blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The antidepressant, antiobsessive-compulsive, and antibulimic actions of fluoxetine are presumed to be linked to its inhibition of CNS neuronal uptake of serotonin. Studies at clinically relevant doses in man have demonstrated that fluoxetine blocks the uptake of serotonin into human platelets. Studies in animals also suggest that fluoxetine is a much more potent uptake inhibitor of serotonin than of norepinephrine.

Antagonism of muscarinic, histaminergic, and α_1-adrenergic receptors has been hypothesized to be associated with various anticholinergic, sedative, and cardiovascular effects of classical tricyclic antidepressant (TCA) drugs. Fluoxetine binds to these and other membrane receptors from brain tissue much less potently in vitro than do the tricyclic drugs.

Absorption, Distribution, Metabolism, and Excretion

Systemic bioavailability — In man, following a single oral 40-mg dose, peak plasma concentrations of fluoxetine from 15 to 55 ng/mL are observed after 6 to 8 hours.

The Pulvule, tablet, oral solution, and Prozac Weekly capsule dosage forms of fluoxetine are bioequivalent. Food does not appear to affect the systemic bioavailability of fluoxetine, although it may delay its absorption by 1 to 2 hours, which is probably not clinically significant. Thus, fluoxetine may be administered with or without food. Prozac Weekly capsules, a delayed release formulation, contain enteric-coated pellets that resist dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. The enteric coating delays the onset of absorption of fluoxetine 1 to 2 hours relative to the immediate release formulations.

Protein binding — Over the concentration range from 200 to 1000 ng/mL, approximately 94.5% of fluoxetine is bound in vitro to human serum proteins, including albumin and α_1-glycoprotein. The interaction between fluoxetine and other highly protein-bound drugs has not been fully evaluated, but may be important (*see* PRECAUTIONS).

Enantiomers — Fluoxetine is a racemic mixture (50/50) of *R*-fluoxetine and *S*-fluoxetine enantiomers. In animal models, both enantiomers are specific and potent serotonin uptake inhibitors with essentially equivalent pharmacologic activity. The *S*-fluoxetine enantiomer is eliminated more slowly and is the predominant enantiomer present in plasma at steady state.

Metabolism — Fluoxetine is extensively metabolized in the liver to norfluoxetine and a number of other unidentified metabolites. The only identified active metabolite, norfluoxetine, is formed by demethylation of fluoxetine. In animal models, *S*-norfluoxetine is a potent and selective inhibitor of serotonin uptake and has activity essentially equivalent to *R*- or *S*-fluoxetine. *R*-norfluoxetine is significantly less potent than the parent drug in the inhibition of serotonin uptake. The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Clinical issues related to metabolism/elimination — The complexity of the metabolism of fluoxetine has several consequences that may potentially affect fluoxetine's clinical use.

Variability in metabolism — A subset (about 7%) of the population has reduced activity of the drug metabolizing enzyme cytochrome P450 2D6 (CYP2D6). Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and the TCAs. In a study involving labeled and unlabeled enantiomers administered as a racemate, these individuals metabolized *S*-fluoxetine at a slower rate and thus achieved higher concentrations of *S*-fluoxetine. Consequently, concentrations of *S*-norfluoxetine at steady state were lower. The metabolism of *R*-fluoxetine in these poor metabolizers appears normal. When compared with normal metabolizers, the total sum at steady state of the plasma concentrations of the 4 active enantiomers was not significantly greater among poor metabolizers. Thus, the net pharmacodynamic activities were essentially the same. Alternative, nonsaturable pathways (non-2D6) also contribute to the metabolism of fluoxetine. This explains how fluoxetine achieves a steady-state concentration rather than increasing without limit.

Because fluoxetine's metabolism, like that of a number of other compounds including TCAs and other SSRIs, involves the CYP2D6 system, concomitant therapy with drugs also metabolized by this enzyme system (such as the TCAs) may lead to drug interactions (*see* Drug Interactions *under* PRECAUTIONS).

Accumulation and slow elimination — The relatively slow elimination of fluoxetine (elimination half-life of 1 to 3 days after acute administration and 4 to 6 days after chronic administration) and its active metabolite, norfluoxetine (elimination half-life of 4 to 16 days after acute and chronic administration), leads to significant accumulation of these active species in chronic use and delayed attainment of steady state, even when a fixed dose is used. After 30 days of dosing at 40 mg/day, plasma concentrations of fluoxetine in the range of 91 to 302 ng/mL and norfluoxetine in the range of 72 to 258 ng/mL have been observed. Plasma concentrations of

fluoxetine were higher than those predicted by single-dose studies, because fluoxetine's metabolism is not proportional to dose. Norfluoxetine, however, appears to have linear pharmacokinetics. Its mean terminal half-life after a single dose was 8.6 days and after multiple dosing was 9.3 days. Steady-state levels after prolonged dosing are similar to levels seen at 4 to 5 weeks.

The long elimination half-lives of fluoxetine and norfluoxetine assure that, even when dosing is stopped, active drug substance will persist in the body for weeks (primarily depending on individual patient characteristics, previous dosing regimen, and length of previous therapy at discontinuation). This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following the discontinuation of Prozac.

Weekly dosing — Administration of Prozac Weekly once-weekly results in increased fluctuation between peak and trough concentrations of fluoxetine and norfluoxetine compared with once-daily dosing [for fluoxetine: 24% (daily) to 164% (weekly) and for norfluoxetine: 17% (daily) to 43% (weekly)]. Plasma concentrations may not necessarily be predictive of clinical response. Peak concentrations from once-weekly doses of Prozac Weekly capsules of fluoxetine are in the range of the average concentration for 20 mg once-daily dosing. Average trough concentrations are 76% lower for fluoxetine and 47% lower for norfluoxetine than the concentrations maintained by 20 mg once-daily dosing. Average steady-state concentrations of either once-daily or once-weekly dosing are in relative proportion to the total dose administered. Average steady-state fluoxetine concentrations are approximately 50% lower following the once-weekly regimen compared with the once-daily regimen.

C_{max} for fluoxetine following the 90-mg dose was approximately 1.7-fold higher than the C_{max} value for the established 20 mg once-daily regimen following transition the next day to the once-weekly regimen. In contrast, when the first 90-mg once-weekly dose and the last 20-mg once-daily dose were separated by 1 week, C_{max} values were similar. Also, there was a transient increase in the average steady-state concentrations of fluoxetine observed following transition the next day to the once-weekly regimen. From a pharmacokinetic perspective, it may be better to separate the first 90-mg weekly dose and the last 20-mg once-daily dose by 1 week (*see* DOSAGE AND ADMINISTRATION).

Liver disease — As might be predicted from its primary site of metabolism, liver impairment can affect the elimination of fluoxetine. The elimination half-life of fluoxetine was prolonged in a study of cirrhotic patients, with a mean of 7.6 days compared with the range of 2 to 3 days seen in subjects without liver disease; norfluoxetine elimination was also delayed, with a mean duration of 12 days for cirrhotic patients compared with the range of 7 to 9 days in normal subjects. This suggests that the use of fluoxetine in patients with liver disease must be approached with caution. If fluoxetine is administered to patients with liver disease, a lower or less frequent dose should be used (*see* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Renal disease — In depressed patients on dialysis (N=12), fluoxetine administered as 20 mg once daily for 2 months produced steady-state fluoxetine and norfluoxetine plasma concentrations comparable with those seen in patients with normal renal function. While the possibility exists that renally excreted metabolites of fluoxetine may accumulate to higher levels in patients with severe renal dysfunction, use of a lower or less frequent dose is not routinely necessary in renally impaired patients (*see* Use in patients with concomitant illness *under* PRECAUTIONS *and* DOSAGE AND ADMINISTRATION).

Age

Geriatric pharmacokinetics — The disposition of single doses of fluoxetine in healthy elderly subjects (>65 years of age) did not differ significantly from that in younger normal subjects. However, given the long half-life and nonlinear disposition of the drug, a single-dose study is not

adequate to rule out the possibility of altered pharmacokinetics in the elderly, particularly if they have systemic illness or are receiving multiple drugs for concomitant diseases. The effects of age upon the metabolism of fluoxetine have been investigated in 260 elderly but otherwise healthy depressed patients (≥60 years of age) who received 20 mg fluoxetine for 6 weeks. Combined fluoxetine plus norfluoxetine plasma concentrations were 209.3 ± 85.7 ng/mL at the end of 6 weeks. No unusual age-associated pattern of adverse events was observed in those elderly patients.

Pediatric pharmacokinetics (children and adolescents) — Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (10 children ages 6 to <13, 11 adolescents ages 13 to <18) diagnosed with major depressive disorder or obsessive compulsive disorder (OCD). Fluoxetine 20 mg/day was administered for up to 62 days. The average steady-state concentrations of fluoxetine in these children were 2-fold higher than in adolescents (171 and 86 ng/mL, respectively). The average norfluoxetine steady-state concentrations in these children were 1.5-fold higher than in adolescents (195 and 113 ng/mL, respectively). These differences can be almost entirely explained by differences in weight. No gender-associated difference in fluoxetine pharmacokinetics was observed. Similar ranges of fluoxetine and norfluoxetine plasma concentrations were observed in another study in 94 pediatric patients (ages 8 to <18) diagnosed with major depressive disorder.

Higher average steady-state fluoxetine and norfluoxetine concentrations were observed in children relative to adults; however, these concentrations were within the range of concentrations observed in the adult population. As in adults, fluoxetine and norfluoxetine accumulated extensively following multiple oral dosing; steady-state concentrations were achieved within 3 to 4 weeks of daily dosing.

CLINICAL TRIALS

Major Depressive Disorder

Daily Dosing

Adult — The efficacy of Prozac for the treatment of patients with major depressive disorder (≥18 years of age) has been studied in 5- and 6-week placebo-controlled trials. Prozac was shown to be significantly more effective than placebo as measured by the Hamilton Depression Rating Scale (HAM-D). Prozac was also significantly more effective than placebo on the HAM-D subscores for depressed mood, sleep disturbance, and the anxiety subfactor.

Two 6-week controlled studies (N=671, randomized) comparing Prozac 20 mg and placebo have shown Prozac 20 mg daily to be effective in the treatment of elderly patients (≥60 years of age) with major depressive disorder. In these studies, Prozac produced a significantly higher rate of response and remission as defined, respectively, by a 50% decrease in the HAM-D score and a total endpoint HAM-D score of ≤8. Prozac was well tolerated and the rate of treatment discontinuations due to adverse events did not differ between Prozac (12%) and placebo (9%).

A study was conducted involving depressed outpatients who had responded (modified HAMD-17 score of ≤7 during each of the last 3 weeks of open-label treatment and absence of major depressive disorder by DSM-III-R criteria) by the end of an initial 12-week open-treatment phase on Prozac 20 mg/day. These patients (N=298) were randomized to continuation on double-blind Prozac 20 mg/day or placebo. At 38 weeks (50 weeks total), a statistically significantly lower relapse rate (defined as symptoms sufficient to meet a diagnosis of major depressive disorder for 2 weeks or a modified HAMD-17 score of ≥14 for 3 weeks) was observed for patients taking Prozac compared with those on placebo.

Pediatric (children and adolescents) — The efficacy of Prozac 20 mg/day for the treatment of major depressive disorder in pediatric outpatients (N=315 randomized; 170 children ages 8 to <13, 145 adolescents ages 13 to ≤18) has been studied in two 8- to 9-week placebo-controlled clinical trials.

In both studies independently, Prozac produced a statistically significantly greater mean change on the Childhood Depression Rating Scale-Revised (CDRS-R) total score from baseline to endpoint than did placebo.

Subgroup analyses on the CDRS-R total score did not suggest any differential responsiveness on the basis of age or gender.

Weekly dosing for maintenance/continuation treatment

A longer-term study was conducted involving adult outpatients meeting DSM-IV criteria for major depressive disorder who had responded (defined as having a modified HAMD-17 score of ≤9, a CGI-Severity rating of ≤2, and no longer meeting criteria for major depressive disorder) for 3 consecutive weeks at the end of 13 weeks of open-label treatment with Prozac 20 mg once daily. These patients were randomized to double-blind, once-weekly continuation treatment with Prozac Weekly, Prozac 20 mg once daily, or placebo. Prozac Weekly once weekly and Prozac 20 mg once daily demonstrated superior efficacy (having a significantly longer time to relapse of depressive symptoms) compared with placebo for a period of 25 weeks. However, the equivalence of these 2 treatments during continuation therapy has not been established.

Obsessive Compulsive Disorder

Adult — The effectiveness of Prozac for the treatment for obsessive compulsive disorder (OCD) was demonstrated in two 13-week, multicenter, parallel group studies (Studies 1 and 2) of adult outpatients who received fixed Prozac doses of 20, 40, or 60 mg/day (on a once-a-day schedule, in the morning) or placebo. Patients in both studies had moderate to severe OCD (DSM-III-R), with mean baseline ratings on the Yale-Brown Obsessive Compulsive Scale (YBOCS, total score) ranging from 22 to 26. In Study 1, patients receiving Prozac experienced mean reductions of approximately 4 to 6 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. In Study 2, patients receiving Prozac experienced mean reductions of approximately 4 to 9 units on the YBOCS total score, compared with a 1-unit reduction for placebo patients. While there was no indication of a dose-response relationship for effectiveness in Study 1, a dose-response relationship was observed in Study 2, with numerically better responses in the 2 higher dose groups. The following table provides the outcome classification by treatment group on the Clinical Global Impression (CGI) improvement scale for Studies 1 and 2 combined:

Outcome Classification (%) on CGI Improvement Scale for Completers in Pool of Two OCD Studies				
		Prozac		
Outcome Classification	Placebo	20 mg	40 mg	60 mg
Worse	8%	0%	0%	0%
No change	64%	41%	33%	29%
Minimally improved	17%	23%	28%	24%
Much improved	8%	28%	27%	28%
Very much improved	3%	8%	12%	19%

Exploratory analyses for age and gender effects on outcome did not suggest any differential responsiveness on the basis of age or sex.

Pediatric (children and adolescents) — In one 13-week clinical trial in pediatric patients (N=103 randomized; 75 children ages 7 to <13, 28 adolescents ages 13 to <18) with OCD, patients received Prozac 10 mg/day for 2 weeks, followed by 20 mg/day for 2 weeks. The dose was then adjusted in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. Prozac produced a statistically significantly greater mean change from baseline to

endpoint than did placebo as measured by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS).

Subgroup analyses on outcome did not suggest any differential responsiveness on the basis of age or gender.

Bulimia Nervosa

The effectiveness of Prozac for the treatment of bulimia was demonstrated in two 8-week and one 16-week, multicenter, parallel group studies of adult outpatients meeting DSM-III-R criteria for bulimia. Patients in the 8-week studies received either 20 or 60 mg/day of Prozac or placebo in the morning. Patients in the 16-week study received a fixed Prozac dose of 60 mg/day (once a day) or placebo. Patients in these 3 studies had moderate to severe bulimia with median binge-eating and vomiting frequencies ranging from 7 to 10 per week and 5 to 9 per week, respectively. In these 3 studies, Prozac 60 mg, but not 20 mg, was statistically significantly superior to placebo in reducing the number of binge-eating and vomiting episodes per week. The statistically significantly superior effect of 60 mg vs placebo was present as early as Week 1 and persisted throughout each study. The Prozac-related reduction in bulimic episodes appeared to be independent of baseline depression as assessed by the Hamilton Depression Rating Scale. In each of these 3 studies, the treatment effect, as measured by differences between Prozac 60 mg and placebo on median reduction from baseline in frequency of bulimic behaviors at endpoint, ranged from 1 to 2 episodes per week for binge-eating and 2 to 4 episodes per week for vomiting. The size of the effect was related to baseline frequency, with greater reductions seen in patients with higher baseline frequencies. Although some patients achieved freedom from binge-eating and purging as a result of treatment, for the majority, the benefit was a partial reduction in the frequency of binge-eating and purging.

In a longer-term trial, 150 patients meeting (DSM-IV) criteria for bulimia nervosa, purging subtype, who had responded during a single-blind, 8-week acute treatment phase with Prozac 60 mg/day, were randomized to continuation of Prozac 60 mg/day or placebo, for up to 52 weeks of observation for relapse. Response during the single-blind phase was defined by having achieved at least a 50% decrease in vomiting frequency compared with baseline. Relapse during the double-blind phase was defined as a persistent return to baseline vomiting frequency or physician judgement that the patient had relapsed. Patients receiving continued Prozac 60 mg/day experienced a significantly longer time to relapse over the subsequent 52 weeks compared with those receiving placebo.

Panic Disorder

The effectiveness of Prozac in the treatment of panic disorder was demonstrated in 2 double-blind, randomized, placebo-controlled, multicenter studies of adult outpatients who had a primary diagnosis of panic disorder (DSM-IV), with or without agoraphobia.

Study 1 (N=180 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in the range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 42% vs 28%, respectively.

Study 2 (N=214 randomized) was a 12-week flexible-dose study. Prozac was initiated at 10 mg/day for the first week, after which patients were dosed in a range of 20 to 60 mg/day on the basis of clinical response and tolerability. A statistically significantly greater percentage of Prozac-treated patients were free from panic attacks at endpoint than placebo-treated patients, 62% vs 44%, respectively.

INDICATIONS AND USAGE

Major Depressive Disorder

Prozac is indicated for the treatment of major depressive disorder.

Adult — The efficacy of Prozac was established in 5- and 6-week trials with depressed adult and geriatric outpatients (≥18 years of age) whose diagnoses corresponded most closely to the DSM-III (currently DSM-IV) category of major depressive disorder (*see* CLINICAL TRIALS).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation.

The effects of Prozac in hospitalized depressed patients have not been adequately studied.

The efficacy of Prozac 20 mg once daily in maintaining a response in major depressive disorder for up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) was demonstrated in a placebo-controlled trial.

The efficacy of Prozac Weekly once weekly in maintaining a response in major depressive disorder has been demonstrated in a placebo-controlled trial for up to 25 weeks following open-label acute treatment of 13 weeks with Prozac 20 mg daily for a total treatment of 38 weeks. However, it is unknown whether or not Prozac Weekly given on a once-weekly basis provides the same level of protection from relapse as that provided by Prozac 20 mg daily (*see* CLINICAL TRIALS).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in two 8- to 9-week placebo-controlled clinical trials in depressed outpatients whose diagnoses corresponded most closely to the DSM-III-R or DSM-IV category of major depressive disorder (*see* CLINICAL TRIALS).

The usefulness of the drug in adult and pediatric patients receiving fluoxetine for extended periods should be reevaluated periodically.

Obsessive-Compulsive Disorder

Adult — Prozac is indicated for the treatment of obsessions and compulsions in patients with obsessive-compulsive disorder (OCD), as defined in the DSM-III-R; i.e., the obsessions or compulsions cause marked distress, are time-consuming, or significantly interfere with social or occupational functioning.

The efficacy of Prozac was established in 13-week trials with obsessive-compulsive outpatients whose diagnoses corresponded most closely to the DSM-III-R category of OCD (*see* CLINICAL TRIALS).

OCD is characterized by recurrent and persistent ideas, thoughts, impulses, or images (obsessions) that are ego-dystonic and/or repetitive, purposeful, and intentional behaviors (compulsions) that are recognized by the person as excessive or unreasonable.

The effectiveness of Prozac in long-term use, i.e., for more than 13 weeks, has not been systematically evaluated in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Pediatric (children and adolescents) — The efficacy of Prozac in children and adolescents was established in a 13-week, dose titration, clinical trial in patients with OCD, as defined in DSM-IV (*see* CLINICAL TRIALS).

Bulimia Nervosa

Prozac is indicated for the treatment of binge-eating and vomiting behaviors in patients with moderate to severe bulimia nervosa.

The efficacy of Prozac was established in 8- to 16-week trials for adult outpatients with moderate to severe bulimia nervosa, i.e., at least 3 bulimic episodes per week for 6 months (*see* CLINICAL TRIALS).

The efficacy of Prozac 60 mg/day in maintaining a response, in patients with bulimia who responded during an 8-week acute treatment phase while taking Prozac 60 mg/day and were then observed for relapse during a period of up to 52 weeks, was demonstrated in a placebo-controlled trial (*see* CLINICAL TRIALS). Nevertheless, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

Panic Disorder

Prozac is indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks, and associated concern about having additional attacks, worry about the implications or consequences of the attacks, and/or a significant change in behavior related to the attacks.

The efficacy of Prozac was established in two 12-week clinical trials in patients whose diagnoses corresponded to the DSM-IV category of panic disorder (*see* CLINICAL TRIALS).

Panic disorder (DSM-IV) is characterized by recurrent, unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which 4 or more of the following symptoms develop abruptly and reach a peak within 10 minutes: 1) palpitations, pounding heart, or accelerated heart rate; 2) sweating; 3) trembling or shaking; 4) sensations of shortness of breath or smothering; 5) feeling of choking; 6) chest pain or discomfort; 7) nausea or abdominal distress; 8) feeling dizzy, unsteady, lightheaded, or faint; 9) fear of losing control; 10) fear of dying; 11) paresthesias (numbness or tingling sensations); 12) chills or hot flashes.

The effectiveness of Prozac in long-term use, i.e., for more than 12 weeks, has not been established in placebo-controlled trials. Therefore, the physician who elects to use Prozac for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (*see* DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS

Prozac is contraindicated in patients known to be hypersensitive to it.

Monoamine oxidase inhibitors — There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving fluoxetine in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued fluoxetine and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, Prozac should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks [perhaps longer, especially if fluoxetine has been prescribed chronically and/or at higher doses (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY)] should be allowed after stopping Prozac before starting an MAOI.

Thioridazine — Thioridazine should not be administered with Prozac or within a minimum of 5 weeks after Prozac has been discontinued (*see* WARNINGS).

WARNINGS

Rash and possibly allergic events — In US fluoxetine clinical trials as of May 8, 1995, 7% of 10,782 patients developed various types of rashes and/or urticaria. Among the cases of rash and/or urticaria reported in premarketing clinical trials, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with rash include fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely.

In premarketing clinical trials, 2 patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other, a severe desquamating syndrome that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic syndromes suggestive of serum sickness.

Since the introduction of Prozac, systemic events, possibly related to vasculitis and including lupus-like syndrome, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events.

Anaphylactoid events, including bronchospasm, angioedema, laryngospasm, and urticaria alone and in combination, have been reported.

Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom.

Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, Prozac should be discontinued.

Potential interaction with thioridazine — In a study of 19 healthy male subjects, which included 6 slow and 13 rapid hydroxylators of debrisoquin, a single 25-mg oral dose of thioridazine produced a 2.4-fold higher C_{max} and a 4.5-fold higher AUC for thioridazine in the slow hydroxylators compared with the rapid hydroxylators. The rate of debrisoquin hydroxylation is felt to depend on the level of CYP2D6 isozyme activity. Thus, this study suggests that drugs which inhibit CYP2D6, such as certain SSRIs, including fluoxetine, will produce elevated plasma levels of thioridazine (*see* PRECAUTIONS).

Thioridazine administration produces a dose-related prolongation of the QT_c interval, which is associated with serious ventricular arrhythmias, such as torsades de pointes-type arrhythmias, and sudden death. This risk is expected to increase with fluoxetine-induced inhibition of thioridazine metabolism (*see* CONTRAINDICATIONS).

PRECAUTIONS

General

Anxiety and insomnia — In US placebo-controlled clinical trials for major depressive disorder, 12% to 16% of patients treated with Prozac and 7% to 9% of patients treated with placebo reported anxiety, nervousness, or insomnia.

In US placebo-controlled clinical trials for OCD, insomnia was reported in 28% of patients treated with Prozac and in 22% of patients treated with placebo. Anxiety was reported in 14% of patients treated with Prozac and in 7% of patients treated with placebo.

In US placebo-controlled clinical trials for bulimia nervosa, insomnia was reported in 33% of patients treated with Prozac 60 mg, and 13% of patients treated with placebo. Anxiety and nervousness were reported, respectively, in 15% and 11% of patients treated with Prozac 60 mg and in 9% and 5% of patients treated with placebo.

Among the most common adverse events associated with discontinuation (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in US placebo-controlled fluoxetine clinical trials were anxiety (2% in OCD), insomnia (1% in combined indications and 2% in bulimia), and nervousness (1% in major depressive disorder) (*see* Table 3).

Altered appetite and weight — Significant weight loss, especially in underweight depressed or bulimic patients may be an undesirable result of treatment with Prozac.

In US placebo-controlled clinical trials for major depressive disorder, 11% of patients treated with Prozac and 2% of patients treated with placebo reported anorexia (decreased appetite). Weight loss was reported in 1.4% of patients treated with Prozac and in 0.5% of patients treated with placebo. However, only rarely have patients discontinued treatment with Prozac because of anorexia or weight loss (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, 17% of patients treated with Prozac and 10% of patients treated with placebo reported anorexia (decreased appetite). One patient discontinued treatment with Prozac because of anorexia (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for bulimia nervosa, 8% of patients treated with Prozac 60 mg and 4% of patients treated with placebo reported anorexia (decreased appetite). Patients treated with Prozac 60 mg on average lost 0.45 kg compared with a gain of 0.16 kg by patients treated with placebo in the 16-week double-blind trial. Weight change should be monitored during therapy.

Activation of mania/hypomania — In US placebo-controlled clinical trials for major depressive disorder, mania/hypomania was reported in 0.1% of patients treated with Prozac and 0.1% of patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed drugs effective in the treatment of major depressive disorder (*see also* Pediatric Use *under* PRECAUTIONS).

In US placebo-controlled clinical trials for OCD, mania/hypomania was reported in 0.8% of patients treated with Prozac and no patients treated with placebo. No patients reported mania/hypomania in US placebo-controlled clinical trials for bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.7% of 10,782 patients reported mania/hypomania (*see also* Pediatric Use *under* PRECAUTIONS).

Seizures — In US placebo-controlled clinical trials for major depressive disorder, convulsions (or events described as possibly having been seizures) were reported in 0.1% of patients treated with Prozac and 0.2% of patients treated with placebo. No patients reported convulsions in US placebo-controlled clinical trials for either OCD or bulimia. In all US Prozac clinical trials as of May 8, 1995, 0.2% of 10,782 patients reported convulsions. The percentage appears to be similar to that associated with other marketed drugs effective in the treatment of major depressive disorder. Prozac should be introduced with care in patients with a history of seizures.

Suicide — The possibility of a suicide attempt is inherent in major depressive disorder and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Prozac should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

Because of well-established comorbidity between both OCD and major depressive disorder and bulimia and major depressive disorder, the same precautions observed when treating patients with major depressive disorder should be observed when treating patients with OCD or bulimia.

The long elimination half-lives of fluoxetine and its metabolites — Because of the long elimination half-lives of the parent drug and its major active metabolite, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (*see* CLINICAL PHARMACOLOGY *and* DOSAGE AND ADMINISTRATION).

Use in patients with concomitant illness — Clinical experience with Prozac in patients with concomitant systemic illness is limited. Caution is advisable in using Prozac in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Fluoxetine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 312 patients who received Prozac in double-blind trials were retrospectively evaluated; no conduction abnormalities that resulted in heart block were observed. The mean heart rate was reduced by approximately 3 beats/min.

In subjects with cirrhosis of the liver, the clearances of fluoxetine and its active metabolite, norfluoxetine, were decreased, thus increasing the elimination half-lives of these substances. A lower or less frequent dose should be used in patients with cirrhosis.

Studies in depressed patients on dialysis did not reveal excessive accumulation of fluoxetine or norfluoxetine in plasma (*see* Renal disease *under* CLINICAL PHARMACOLOGY). Use of a lower or less frequent dose for renally impaired patients is not routinely necessary (*see* DOSAGE AND ADMINISTRATION).

In patients with diabetes, Prozac may alter glycemic control. Hypoglycemia has occurred during therapy with Prozac, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with Prozac is instituted or discontinued.

Interference with cognitive and motor performance — Any psychoactive drug may impair judgment, thinking, or motor skills, and patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe Prozac:

Because Prozac may impair judgment, thinking, or motor skills, patients should be advised to avoid driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected.

Patients should be advised to inform their physician if they are taking or plan to take any prescription or over-the-counter drugs, or alcohol.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Patients should be advised to notify their physician if they develop a rash or hives.

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

As with all drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic drug inhibition or enhancement, etc.) is a possibility (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Drugs metabolized by CYP2D6 — Approximately 7% of the normal population has a genetic defect that leads to reduced levels of activity of the cytochrome P450 isoenzyme 2D6. Such individuals have been referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, and TCAs. Many drugs, such as most drugs effective in the treatment of major depressive disorder, including fluoxetine and other selective uptake inhibitors of serotonin, are metabolized by this isoenzyme; thus, both the pharmacokinetic properties and relative proportion of metabolites are altered in poor metabolizers. However, for fluoxetine and its metabolite, the sum of the plasma concentrations of the 4 active enantiomers is comparable between poor and extensive metabolizers (*see* Variability in metabolism *under* CLINICAL PHARMACOLOGY).

Fluoxetine, like other agents that are metabolized by CYP2D6, inhibits the activity of this isoenzyme, and thus may make normal metabolizers resemble poor metabolizers. Therapy with medications that are predominantly metabolized by the CYP2D6 system and that have a relatively narrow therapeutic index (see list below) should be initiated at the low end of the dose range if a patient is receiving fluoxetine concurrently or has taken it in the previous 5 weeks. Thus, his/her dosing requirements resemble those of poor metabolizers. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g., flecainide, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine or within a minimum of 5 weeks after fluoxetine has been discontinued (*see* CONTRAINDICATIONS *and* WARNINGS).

Drugs metabolized by CYP3A4 — In an in vivo interaction study involving coadministration of fluoxetine with single doses of terfenadine (a CYP3A4 substrate), no increase in plasma terfenadine concentrations occurred with concomitant fluoxetine. In addition, in vitro studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than fluoxetine or norfluoxetine as an inhibitor of the metabolism of several substrates for this enzyme, including astemizole, cisapride, and midazolam. These data indicate that fluoxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

CNS active drugs — The risk of using Prozac in combination with other CNS active drugs has not been systematically evaluated. Nonetheless, caution is advised if the concomitant administration of Prozac and such drugs is required. In evaluating individual cases, consideration should be given to using lower initial doses of the concomitantly administered drugs, using conservative titration schedules, and monitoring of clinical status (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Anticonvulsants — Patients on stable doses of phenytoin and carbamazepine have developed elevated plasma anticonvulsant concentrations and clinical anticonvulsant toxicity following initiation of concomitant fluoxetine treatment.

Antipsychotics — Some clinical data suggests a possible pharmacodynamic and/or pharmacokinetic interaction between serotonin specific reuptake inhibitors (SSRIs) and antipsychotics. Elevation of blood levels of haloperidol and clozapine has been observed in patients receiving concomitant fluoxetine. A single case report has suggested possible additive effects of pimozide and fluoxetine leading to bradycardia. For thioridazine, see CONTRAINDICATIONS and WARNINGS.

Benzodiazepines — The half-life of concurrently administered diazepam may be prolonged in some patients (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY). Coadministration of alprazolam and fluoxetine has resulted in increased alprazolam plasma concentrations and in further psychomotor performance decrement due to increased alprazolam levels.

Lithium — There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity and increased serotonergic effects have been reported. Lithium levels should be monitored when these drugs are administered concomitantly.

Tryptophan — Five patients receiving Prozac in combination with tryptophan experienced adverse reactions, including agitation, restlessness, and gastrointestinal distress.

Monoamine oxidase inhibitors — See CONTRAINDICATIONS.

Other drugs effective in the treatment of major depressive disorder — In 2 studies, previously stable plasma levels of imipramine and desipramine have increased greater than 2- to 10-fold when fluoxetine has been administered in combination. This influence may persist for 3 weeks or longer after fluoxetine is discontinued. Thus, the dose of TCA may need to be reduced and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY, *and* Drugs metabolized by CYP2D6 *under* Drug Interactions).

Sumatriptan — There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, or citalopram) is clinically warranted, appropriate observation of the patient is advised.

Potential effects of coadministration of drugs tightly bound to plasma proteins — Because fluoxetine is tightly bound to plasma protein, the administration of fluoxetine to a patient taking another drug that is tightly bound to protein (e.g., Coumadin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound fluoxetine by other tightly bound drugs (*see* Accumulation and slow elimination *under* CLINICAL PHARMACOLOGY).

Warfarin — Altered anticoagulant effects, including increased bleeding, have been reported when fluoxetine is coadministered with warfarin. Patients receiving warfarin therapy should receive careful coagulation monitoring when fluoxetine is initiated or stopped.

Electroconvulsive therapy (ECT) — There are no clinical studies establishing the benefit of the combined use of ECT and fluoxetine. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment.

Carcinogenesis, Mutagenesis, Impairment of Fertility

There is no evidence of carcinogenicity, mutagenicity, or impairment of fertility with Prozac.

Carcinogenicity — The dietary administration of fluoxetine to rats and mice for 2 years at doses of up to 10 and 12 mg/kg/day, respectively [approximately 1.2 and 0.7 times, respectively, the maximum recommended human dose (MRHD) of 80 mg on a mg/m^2 basis], produced no evidence of carcinogenicity.

Mutagenicity — Fluoxetine and norfluoxetine have been shown to have no genotoxic effects based on the following assays: bacterial mutation assay, DNA repair assay in cultured rat hepatocytes, mouse lymphoma assay, and in vivo sister chromatid exchange assay in Chinese hamster bone marrow cells.

Impairment of fertility — Two fertility studies conducted in rats at doses of up to 7.5 and 12.5 mg/kg/day (approximately 0.9 and 1.5 times the MRHD on a mg/m^2 basis) indicated that fluoxetine had no adverse effects on fertility.

Pregnancy — Pregnancy Category C

In embryo-fetal development studies in rats and rabbits, there was no evidence of teratogenicity following administration of up to 12.5 and 15 mg/kg/day, respectively (1.5 and 3.6 times, respectively, the MRHD of 80 mg on a mg/m^2 basis) throughout organogenesis. However, in rat reproduction studies, an increase in stillborn pups, a decrease in pup weight, and an increase in pup deaths during the first 7 days postpartum occurred following maternal exposure to 12 mg/kg/day (1.5 times the MRHD on a mg/m^2 basis) during gestation or 7.5 mg/kg/day (0.9 times the MRHD on a mg/m^2 basis) during gestation and lactation. There was no evidence of developmental neurotoxicity in the surviving offspring of rats treated with 12 mg/kg/day during gestation. The no-effect dose for rat pup mortality was 5 mg/kg/day (0.6 times the MRHD on a mg/m^2 basis). Prozac should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of Prozac on labor and delivery in humans is unknown. However, because fluoxetine crosses the placenta and because of the possibility that fluoxetine may have adverse effects on the newborn, fluoxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Because Prozac is excreted in human milk, nursing while on Prozac is not recommended. In 1 breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, an infant nursed by a mother on Prozac developed crying, sleep disturbance, vomiting, and watery stools. The infant's plasma drug levels were 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine on the second day of feeding.

Pediatric Use

The efficacy of Prozac for the treatment of major depressive disorder was demonstrated in two 8- to 9-week placebo-controlled clinical trials with 315 pediatric outpatients ages 8 to ≤18. (*see* CLINICAL TRIALS).

The efficacy of Prozac for the treatment of OCD was demonstrated in one 13-week placebo-controlled clinical trial with 103 pediatric outpatients ages 7 to <18 (*see* CLINICAL TRIALS).

The safety and effectiveness in pediatric patients <8 years of age in major depressive disorder and <7 years of age in OCD have not been established.

Fluoxetine pharmacokinetics were evaluated in 21 pediatric patients (ages 6 to ≤18) with major depressive disorder or OCD (*see* Pharmacokinetics *under* CLINICAL PHARMACOLOGY).

The acute adverse event profiles observed in the 3 studies (N=418 randomized; 228 fluoxetine-treated, 190 placebo-treated) were generally similar to that observed in adult studies with fluoxetine. The longer-term adverse event profile observed in the 19-week major depressive disorder study (N=219 randomized; 109 fluoxetine-treated, 110 placebo-treated) was also similar to that observed in adult trials with fluoxetine (*see* ADVERSE REACTIONS).

Manic reaction, including mania and hypomania, was reported in 6 (1 mania, 5 hypomania) out of 228 (2.6%) fluoxetine-treated patients and in 0 out of 190 (0%) placebo-treated patients. Mania/hypomania led to the discontinuation of 4 (1.8%) fluoxetine-treated patients from the acute phases of the 3 studies combined. Consequently, regular monitoring for the occurrence of mania/hypomania is recommended.

As with other SSRIs, decreased weight gain has been observed in association with the use of fluoxetine in children and adolescent patients. After 19 weeks of treatment in a clinical trial, pediatric subjects treated with fluoxetine gained an average of 1.1 cm less in height (p=0.004)

and 1.1 kg less in weight (p=0.008) than subjects treated with placebo. In addition, fluoxetine treatment was associated with a decrease in alkaline phosphatase levels. The safety of fluoxetine treatment for pediatric patients has not been systematically assessed for chronic treatment longer than several months in duration. In particular, there are no studies that directly evaluate the longer-term effects of fluoxetine on the growth, development, and maturation of children and adolescent patients. Therefore, height and weight should be monitored periodically in pediatric patients receiving fluoxetine.

Geriatric Use

US fluoxetine clinical trials as of May 8, 1995 (10,782 patients) included 687 patients ≥65 years of age and 93 patients ≥75 years of age. The efficacy in geriatric patients has been established (*see* CLINICAL TRIALS). For pharmacokinetic information in geriatric patients, see Age under CLINICAL PHARMACOLOGY. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. As with other SSRIs, fluoxetine has been associated with cases of clinically significant hyponatremia in elderly patients (*see* Hyponatremia *under* PRECAUTIONS).

Hyponatremia

Cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when Prozac was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In two 6-week controlled studies in patients ≥60 years of age, 10 of 323 fluoxetine patients and 6 of 327 placebo recipients had a lowering of serum sodium below the reference range; this difference was not statistically significant. The lowest observed concentration was 129 mmol/L. The observed decreases were not clinically significant.

Platelet Function

There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role.

ADVERSE REACTIONS

Multiple doses of Prozac had been administered to 10,782 patients with various diagnoses in US clinical trials as of May 8, 1995. In addition, there have been 425 patients administered Prozac in panic clinical trials. Adverse events were recorded by clinical investigators using descriptive terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a limited (i.e., reduced) number of standardized event categories.

In the tables and tabulations that follow, COSTART Dictionary terminology has been used to classify reported adverse events. The stated frequencies represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. It is important to emphasize that events reported during therapy were not necessarily caused by it.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient

characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Incidence in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 1 enumerates the most common treatment-emergent adverse events associated with the use of Prozac (incidence of at least 5% for Prozac and at least twice that for placebo within at least 1 of the indications) for the treatment of major depressive disorder, OCD, and bulimia in US controlled clinical trials and panic disorder in US plus non-US controlled trials. Table 2 enumerates treatment-emergent adverse events that occurred in 2% or more patients treated with Prozac and with incidence greater than placebo who participated in US major depressive disorder, OCD, and bulimia controlled clinical trials and US plus non-US panic disorder controlled clinical trials. Table 2 provides combined data for the pool of studies that are provided separately by indication in Table 1.

Table 1: Most Common Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event							
	Major Depressive Disorder		OCD		Bulimia		Panic Disorder	
Body System/ Adverse Event	Prozac (N=1728)	Placebo (N=975)	Prozac (N=266)	Placebo (N=89)	Prozac (N=450)	Placebo (N=267)	Prozac (N=425)	Placebo (N=342)
Body as a Whole								
Asthenia	9	5	15	11	21	9	7	7
Flu syndrome	3	4	10	7	8	3	5	5
Cardiovascular System								
Vasodilatation	3	2	5	--	2	1	1	--
Digestive System								
Nausea	21	9	26	13	29	11	12	7
Diarrhea	12	8	18	13	8	6	9	4
Anorexia	11	2	17	10	8	4	4	1
Dry mouth	10	7	12	3	9	6	4	4
Dyspepsia	7	5	10	4	10	6	6	2
Nervous System								
Insomnia	16	9	28	22	33	13	10	7
Anxiety	12	7	14	7	15	9	6	2
Nervousness	14	9	14	15	11	5	8	6
Somnolence	13	6	17	7	13	5	5	2
Tremor	10	3	9	1	13	1	3	1
Libido decreased	3	--	11	2	5	1	1	2
Abnormal dreams	1	1	5	2	5	3	1	1
Respiratory System								
Pharyngitis	3	3	11	9	10	5	3	3
Sinusitis	1	4	5	2	6	4	2	3
Yawn	--	--	7	--	11	--	1	--
Skin and Appendages								
Sweating	8	3	7	--	8	3	2	2

Rash	4	3	6	3	4	4	2	2
Urogenital System								
Impotence[2]	2	--	--	--	7	--	1	--
Abnormal ejaculation[2]	--	--	7	--	7	--	2	1

[1]Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.
[2]Denominator used was for males only (N=690 Prozac major depressive disorder; N=410 placebo major depressive disorder; N=116 Prozac OCD; N=43 placebo OCD; N=14 Prozac bulimia; N=1 placebo bulimia; N=162 Prozac panic; N=121 placebo panic).
--Incidence less than 1%.

Table 2: Treatment-Emergent Adverse Events: Incidence in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

	Percentage of Patients Reporting Event	
	Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined	
Body System/ Adverse Event[2]	Prozac (N=2869)	Placebo (N=1673)
Body as a Whole		
Headache	21	19
Asthenia	11	6
Flu syndrome	5	4
Fever	2	1
Cardiovascular System		
Vasodilatation	2	1
Digestive System		
Nausea	22	9
Diarrhea	11	7
Anorexia	10	3
Dry mouth	9	6
Dyspepsia	8	4
Constipation	5	4
Flatulence	3	2
Vomiting	3	2
Metabolic and Nutritional Disorders		
Weight loss	2	1
Nervous System		
Insomnia	19	10
Nervousness	13	8
Anxiety	12	6
Somnolence	12	5
Dizziness	9	6
Tremor	9	2
Libido decreased	4	1

Thinking abnormal	2	1
Respiratory System		
Yawn	3	--
Skin and Appendages		
Sweating	7	3
Rash	4	3
Pruritus	3	2
Special Senses		
Abnormal vision	2	1

[1]Includes US data for major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US data for panic disorder clinical trials.

[2]Included are events reported by at least 2% of patients taking Prozac, except the following events, which had an incidence on placebo ≥ Prozac (major depressive disorder, OCD, bulimia, and panic disorder combined): abdominal pain, abnormal dreams, accidental injury, back pain, cough increased, major depressive disorder (includes suicidal thoughts), dysmenorrhea, infection, myalgia, pain, paresthesia, pharyngitis, rhinitis, sinusitis.

--Incidence less than 1%.

Associated with discontinuation in major depressive disorder, OCD, bulimia, and panic disorder placebo-controlled clinical trials (excluding data from extensions of trials) — Table 3 lists the adverse events associated with discontinuation of Prozac treatment (incidence at least twice that for placebo and at least 1% for Prozac in clinical trials collecting only a primary event associated with discontinuation) in major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Table 3: Most Common Adverse Events Associated with Discontinuation in Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Placebo-Controlled Clinical Trials[1]

Major Depressive Disorder, OCD, Bulimia, and Panic Disorder Combined (N=1533)	Major Depressive Disorder (N=392)	OCD (N=266)	Bulimia (N=450)	Panic Disorder (N=425)
Anxiety (1%)	--	Anxiety (2%)	--	Anxiety (2%)
--	--	--	Insomnia (2%)	--
--	Nervousness (1%)	--	--	Nervousness (1%)
--	--	Rash (1%)	--	--

[1]Includes US major depressive disorder, OCD, bulimia, and panic disorder clinical trials, plus non-US panic disorder clinical trials.

Other adverse events in pediatric patients (children and adolescents) — Treatment-emergent adverse events were collected in 322 pediatric patients (180 fluoxetine-treated, 142 placebo-treated). The overall profile of adverse events was generally similar to that seen in adult studies, as shown in Tables 1 and 2. However, the following adverse events (excluding those which appear in the body or footnotes of Tables 1 and 2 and those for which the COSTART terms were uninformative or misleading) were reported at an incidence of at least 2% for fluoxetine and greater than placebo: thirst, hyperkinesia, agitation, personality disorder, epistaxis, urinary frequency, and menorrhagia.

The most common adverse event (incidence at least 1% for fluoxetine and greater than placebo) associated with discontinuation in 3 pediatric placebo-controlled trials (N=418 randomized; 228 fluoxetine-treated; 190 placebo-treated) was mania/hypomania (1.8% for

fluoxetine-treated, 0% for placebo-treated). In these clinical trials, only a primary event associated with discontinuation was collected.

Events observed in Prozac Weekly clinical trials — Treatment-emergent adverse events in clinical trials with Prozac Weekly were similar to the adverse events reported by patients in clinical trials with Prozac daily. In a placebo-controlled clinical trial, more patients taking Prozac Weekly reported diarrhea than patients taking placebo (10% vs 3%, respectively) or taking Prozac 20 mg daily (10% vs 5%, respectively).

Male and female sexual dysfunction with SSRIs — Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance, cited in product labeling, are likely to underestimate their actual incidence. In patients enrolled in US major depressive disorder, OCD, and bulimia placebo-controlled clinical trials, decreased libido was the only sexual side effect reported by at least 2% of patients taking fluoxetine (4% fluoxetine, <1% placebo). There have been spontaneous reports in women taking fluoxetine of orgasmic dysfunction, including anorgasmia.

There are no adequate and well-controlled studies examining sexual dysfunction with fluoxetine treatment.

Priapism has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Other Events Observed in Clinical Trials

Following is a list of all treatment-emergent adverse events reported at anytime by individuals taking fluoxetine in US clinical trials as of May 8, 1995 (10,782 patients) except (1) those listed in the body or footnotes of Tables 1 or 2 above or elsewhere in labeling; (2) those for which the COSTART terms were uninformative or misleading; (3) those events for which a causal relationship to Prozac use was considered remote; and (4) events occurring in only 1 patient treated with Prozac and which did not have a substantial probability of being acutely life-threatening.

Events are classified within body system categories using the following definitions: frequent adverse events are defined as those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in less than 1/1000 patients.

Body as a Whole — *Frequent:* chest pain, chills; *Infrequent:* chills and fever, face edema, intentional overdose, malaise, pelvic pain, suicide attempt; *Rare:* abdominal syndrome acute, hypothermia, intentional injury, neuroleptic malignant syndrome[1], photosensitivity reaction.

Cardiovascular System — *Frequent:* hemorrhage, hypertension, palpitation; *Infrequent:* angina pectoris, arrhythmia, congestive heart failure, hypotension, migraine, myocardial infarct, postural hypotension, syncope, tachycardia, vascular headache; *Rare:* atrial fibrillation, bradycardia, cerebral embolism, cerebral ischemia, cerebrovascular accident, extrasystoles, heart arrest, heart block, pallor, peripheral vascular disorder, phlebitis, shock, thrombophlebitis, thrombosis, vasospasm, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation.

Digestive System — *Frequent:* increased appetite, nausea and vomiting; *Infrequent:* aphthous stomatitis, cholelithiasis, colitis, dysphagia, eructation, esophagitis, gastritis, gastroenteritis, glossitis, gum hemorrhage, hyperchlorhydria, increased salivation, liver function tests abnormal, melena, mouth ulceration, nausea/vomiting/diarrhea, stomach ulcer, stomatitis, thirst; *Rare:*

biliary pain, bloody diarrhea, cholecystitis, duodenal ulcer, enteritis, esophageal ulcer, fecal incontinence, gastrointestinal hemorrhage, hematemesis, hemorrhage of colon, hepatitis, intestinal obstruction, liver fatty deposit, pancreatitis, peptic ulcer, rectal hemorrhage, salivary gland enlargement, stomach ulcer hemorrhage, tongue edema.

Endocrine System — *Infrequent:* hypothyroidism; *Rare:* diabetic acidosis, diabetes mellitus.

Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis; *Rare:* blood dyscrasia, hypochromic anemia, leukopenia, lymphedema, lymphocytosis, petechia, purpura, thrombocythemia, thrombocytopenia.

Metabolic and Nutritional — *Frequent:* weight gain; *Infrequent:* dehydration, generalized edema, gout, hypercholesteremia, hyperlipemia, hypokalemia, peripheral edema; *Rare:* alcohol intolerance, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, hyperkalemia, hyperuricemia, hypocalcemia, iron deficiency anemia, SGPT increased.

Musculoskeletal System — *Infrequent:* arthritis, bone pain, bursitis, leg cramps, tenosynovitis; *Rare:* arthrosis, chondrodystrophy, myasthenia, myopathy, myositis, osteomyelitis, osteoporosis, rheumatoid arthritis.

Nervous System — *Frequent:* agitation, amnesia, confusion, emotional lability, sleep disorder; *Infrequent:* abnormal gait, acute brain syndrome, akathisia, apathy, ataxia, buccoglossal syndrome, CNS depression, CNS stimulation, depersonalization, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, hypesthesia, incoordination, libido increased, myoclonus, neuralgia, neuropathy, neurosis, paranoid reaction, personality disorder[2], psychosis, vertigo; *Rare:* abnormal electroencephalogram, antisocial reaction, circumoral paresthesia, coma, delusions, dysarthria, dystonia, extrapyramidal syndrome, foot drop, hyperesthesia, neuritis, paralysis, reflexes decreased, reflexes increased, stupor.

Respiratory System — *Infrequent:* asthma, epistaxis, hiccup, hyperventilation; *Rare:* apnea, atelectasis, cough decreased, emphysema, hemoptysis, hypoventilation, hypoxia, larynx edema, lung edema, pneumothorax, stridor.

Skin and Appendages — *Infrequent:* acne, alopecia, contact dermatitis, eczema, maculopapular rash, skin discoloration, skin ulcer, vesiculobullous rash; *Rare:* furunculosis, herpes zoster, hirsutism, petechial rash, psoriasis, purpuric rash, pustular rash, seborrhea.

Special Senses — *Frequent:* ear pain, taste perversion, tinnitus; *Infrequent:* conjunctivitis, dry eyes, mydriasis, photophobia; *Rare:* blepharitis, deafness, diplopia, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, iritis, parosmia, scleritis, strabismus, taste loss, visual field defect.

Urogenital System — *Frequent:* urinary frequency; *Infrequent:* abortion[3], albuminuria, amenorrhea[3], anorgasmia, breast enlargement, breast pain, cystitis, dysuria, female lactation[3], fibrocystic breast[3], hematuria, leukorrhea[3], menorrhagia[3], metrorrhagia[3], nocturia, polyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage[3]; *Rare:* breast engorgement, glycosuria, hypomenorrhea[3], kidney pain, oliguria, priapism[3], uterine hemorrhage[3], uterine fibroids enlarged[3].

[1]Neuroleptic malignant syndrome is the COSTART term which best captures serotonin syndrome.
[2]Personality disorder is the COSTART term for designating non-aggressive objectionable behavior.
[3]Adjusted for gender.

Postintroduction Reports

Voluntary reports of adverse events temporally associated with Prozac that have been received since market introduction and that may have no causal relationship with the drug include the following: aplastic anemia, atrial fibrillation, cataract, cerebral vascular accident, cholestatic jaundice, confusion, dyskinesia (including, for example, a case of buccal-lingual-masticatory syndrome with involuntary tongue protrusion reported to develop in a 77-year-old female after 5 weeks of fluoxetine therapy and which completely resolved over the next few months following drug discontinuation), eosinophilic pneumonia, epidermal necrolysis, erythema

nodosum, exfoliative dermatitis, gynecomastia, heart arrest, hepatic failure/necrosis, hyperprolactinemia, hypoglycemia, immune-related hemolytic anemia, kidney failure, misuse/abuse, movement disorders developing in patients with risk factors including drugs associated with such events and worsening of preexisting movement disorders, neuroleptic malignant syndrome-like events, optic neuritis, pancreatitis, pancytopenia, priapism, pulmonary embolism, pulmonary hypertension, QT prolongation, serotonin syndrome (a range of signs and symptoms that can rarely, in its most severe form, resemble neuroleptic malignant syndrome), Stevens-Johnson syndrome, sudden unexpected death, suicidal ideation, thrombocytopenia, thrombocytopenic purpura, vaginal bleeding after drug withdrawal, ventricular tachycardia (including torsades de pointes-type arrhythmias), and violent behaviors.

DRUG ABUSE AND DEPENDENCE

Controlled substance class — Prozac is not a controlled substance.

Physical and psychological dependence — Prozac has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. While the premarketing clinical experience with Prozac did not reveal any tendency for a withdrawal syndrome or any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Prozac (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE

Human Experience

Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients (circa 1999). Of the 1578 cases of overdose involving fluoxetine hydrochloride, alone or with other drugs, reported from this population, there were 195 deaths.

Among 633 adult patients who overdosed on fluoxetine hydrochloride alone, 34 resulted in a fatal outcome, 378 completely recovered, and 15 patients experienced sequelae after overdosage, including abnormal accommodation, abnormal gait, confusion, unresponsiveness, nervousness, pulmonary dysfunction, vertigo, tremor, elevated blood pressure, impotence, movement disorder, and hypomania. The remaining 206 patients had an unknown outcome. The most common signs and symptoms associated with non-fatal overdosage were seizures, somnolence, nausea, tachycardia, and vomiting. The largest known ingestion of fluoxetine hydrochloride in adult patients was 8 grams in a patient who took fluoxetine alone and who subsequently recovered. However, in an adult patient who took fluoxetine alone, an ingestion as low as 520 mg has been associated with lethal outcome, but causality has not been established.

Among pediatric patients (ages 3 months to 17 years), there were 156 cases of overdose involving fluoxetine alone or in combination with other drugs. Six patients died, 127 patients completely recovered, 1 patient experienced renal failure, and 22 patients had an unknown outcome. One of the six fatalities was a 9-year-old boy who had a history of OCD, Tourette's syndrome with tics, attention deficit disorder, and fetal alcohol syndrome. He had been receiving 100 mg of fluoxetine daily for 6 months in addition to clonidine, methylphenidate, and promethazine. Mixed-drug ingestion or other methods of suicide complicated all 6 overdoses in children that resulted in fatalities. The largest ingestion in pediatric patients was 3 grams which was non-lethal.

Other important adverse events reported with fluoxetine overdose (single or multiple drugs) include coma, delirium, ECG abnormalities (such as QT interval prolongation and ventricular tachycardia, including torsades de pointes-type arrhythmias), hypotension, mania, neuroleptic malignant syndrome-like events, pyrexia, stupor, and syncope.

Animal Experience

Studies in animals do not provide precise or necessarily valid information about the treatment of human overdose. However, animal experiments can provide useful insights into possible treatment strategies.

The oral median lethal dose in rats and mice was found to be 452 and 248 mg/kg, respectively. Acute high oral doses produced hyperirritability and convulsions in several animal species.

Among 6 dogs purposely overdosed with oral fluoxetine, 5 experienced grand mal seizures. Seizures stopped immediately upon the bolus intravenous administration of a standard veterinary dose of diazepam. In this short-term study, the lowest plasma concentration at which a seizure occurred was only twice the maximum plasma concentration seen in humans taking 80 mg/day, chronically.

In a separate single-dose study, the ECG of dogs given high doses did not reveal prolongation of the PR, QRS, or QT intervals. Tachycardia and an increase in blood pressure were observed. Consequently, the value of the ECG in predicting cardiac toxicity is unknown. Nonetheless, the ECG should ordinarily be monitored in cases of human overdose (*see* Management of Overdose).

Management of Overdose

Treatment should consist of those general measures employed in the management of overdosage with any drug effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluoxetine are known.

A specific caution involves patients who are taking or have recently taken fluoxetine and might ingest excessive quantities of a TCA. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (*see* Other drugs effective in the treatment of major depressive disorder *under* PRECAUTIONS).

Based on experience in animals, which may not be relevant to humans, fluoxetine-induced seizures that fail to remit spontaneously may respond to diazepam.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (*PDR*).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Initial Treatment

Adult — In controlled trials used to support the efficacy of fluoxetine, patients were administered morning doses ranging from 20 to 80 mg/day. Studies comparing fluoxetine 20, 40, and 60 mg/day to placebo indicate that 20 mg/day is sufficient to obtain a satisfactory response in major depressive disorder in most cases. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose.

A dose increase may be considered after several weeks if insufficient clinical improvement is observed. Doses above 20 mg/day may be administered on a once-a-day (morning) or BID schedule (i.e., morning and noon) and should not exceed a maximum dose of 80 mg/day.

Pediatric (children and adolescents) — In the short-term (8 to 9 week) controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of major depressive disorder, patients were administered fluoxetine doses of 10 to 20 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 or 20 mg/day. After 1 week at 10 mg/day, the dose should be increased to 20 mg/day.

However, due to higher plasma levels in lower weight children, the starting and target dose in this group may be 10 mg/day. A dose increase to 20 mg/day may be considered after several weeks if insufficient clinical improvement is observed.

All patients — As with other drugs effective in the treatment of major depressive disorder, the full effect may be delayed until 4 weeks of treatment or longer.

As with many other medications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Daily Dosing

Systematic evaluation of Prozac in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 38 weeks following 12 weeks of open-label acute treatment (50 weeks total) at a dose of 20 mg/day (*see* CLINICAL TRIALS).

Weekly Dosing

Systematic evaluation of Prozac Weekly in adult patients has shown that its efficacy in major depressive disorder is maintained for periods of up to 25 weeks with once-weekly dosing following 13 weeks of open-label treatment with Prozac 20 mg once daily. However, therapeutic equivalence of Prozac Weekly given on a once-weekly basis with Prozac 20 mg given daily for delaying time to relapse has not been established (*see* CLINICAL TRIALS).

Weekly dosing with Prozac Weekly capsules is recommended to be initiated 7 days after the last daily dose of Prozac 20 mg (*see* Weekly dosing *under* CLINICAL PHARMACOLOGY).

If satisfactory response is not maintained with Prozac Weekly, consider reestablishing a daily dosing regimen (*see* CLINICAL TRIALS).

Switching Patients to a Tricyclic Antidepressant (TCA)

Dosage of a TCA may need to be reduced, and plasma TCA concentrations may need to be monitored temporarily when fluoxetine is coadministered or has been recently discontinued (*see* Other drugs effective in the treatment of major depressive disorder *under* Drug Interactions).

Switching Patients to or from a Monoamine Oxidase Inhibitor (MAOI)

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Prozac. In addition, at least 5 weeks, perhaps longer, should be allowed after stopping Prozac before starting an MAOI (*see* CONTRAINDICATIONS *and* PRECAUTIONS).

Obsessive-Compulsive Disorder

Initial Treatment

Adult — In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fixed daily doses of 20, 40, or 60 mg of fluoxetine

or placebo (*see* CLINICAL TRIALS). In 1 of these studies, no dose-response relationship for effectiveness was demonstrated. Consequently, a dose of 20 mg/day, administered in the morning, is recommended as the initial dose. Since there was a suggestion of a possible dose-response relationship for effectiveness in the second study, a dose increase may be considered after several weeks if insufficient clinical improvement is observed. The full therapeutic effect may be delayed until 5 weeks of treatment or longer.

Doses above 20 mg/day may be administered on a once-a-day (i.e., morning) or BID schedule (i.e., morning and noon). A dose range of 20 to 60 mg/day is recommended; however, doses of up to 80 mg/day have been well tolerated in open studies of OCD. The maximum fluoxetine dose should not exceed 80 mg/day.

Pediatric (children and adolescents) — In the controlled clinical trial of fluoxetine supporting its effectiveness in the treatment of OCD, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS).

In adolescents and higher weight children, treatment should be initiated with a dose of 10 mg/day. After 2 weeks, the dose should be increased to 20 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 60 mg/day is recommended.

In lower weight children, treatment should be initiated with dose of 10 mg/day. Additional dose increases may be considered after several more weeks if insufficient clinical improvement is observed. A dose range of 20 to 30 mg/day is recommended. Experience with daily doses greater than 20 mg is very minimal, and there is no experience with doses greater than 60 mg.

All patients — As with the use of Prozac in the treatment of major depressive disorder, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, OCD is a chronic condition and it is reasonable to consider continuation for a responding patient. Although the efficacy of Prozac after 13 weeks has not been documented in controlled trials, adult patients have been continued in therapy under double-blind conditions for up to an additional 6 months without loss of benefit. However, dosage adjustments should be made to maintain the patient on the lowest effective dosage, and patients should be periodically reassessed to determine the need for treatment.

Bulimia Nervosa

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of bulimia nervosa, patients were administered fixed daily fluoxetine doses of 20 or 60 mg, or placebo (*see* CLINICAL TRIALS). Only the 60-mg dose was statistically significantly superior to placebo in reducing the frequency of binge-eating and vomiting. Consequently, the recommended dose is 60 mg/day, administered in the morning. For some patients it may be advisable to titrate up to this target dose over several days. Fluoxetine doses above 60 mg/day have not been systematically studied in patients with bulimia.

As with the use of Prozac in the treatment of major depressive disorder and OCD, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments

for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

Systematic evaluation of continuing Prozac 60 mg/day for periods of up to 52 weeks in patients with bulimia who have responded while taking Prozac 60 mg/day during an 8-week acute treatment phase has demonstrated a benefit of such maintenance treatment (*see* CLINICAL TRIALS). Nevertheless, patients should be periodically reassessed to determine the need for maintenance treatment.

Panic Disorder

Initial Treatment

In the controlled clinical trials of fluoxetine supporting its effectiveness in the treatment of panic disorder, patients were administered fluoxetine doses in the range of 10 to 60 mg/day (*see* CLINICAL TRIALS). Treatment should be initiated with a dose of 10 mg/day. After 1 week, the dose should be increased to 20 mg/day. The most frequently administered dose in the 2 flexible-dose clinical trials was 20 mg/day.

A dose increase may be considered after several weeks if no clinical improvement is observed. Fluoxetine doses above 60 mg/day have not been systematically evaluated in patients with panic disorder.

As with the use of Prozac in other indications, a lower or less frequent dosage should be used in patients with hepatic impairment. A lower or less frequent dosage should also be considered for the elderly (*see* Geriatric Use *under* PRECAUTIONS), and for patients with concurrent disease or on multiple concomitant medications. Dosage adjustments for renal impairment are not routinely necessary (*see* Liver disease *and* Renal disease *under* CLINICAL PHARMACOLOGY, *and* Use in patients with concomitant illness *under* PRECAUTIONS).

Maintenance/Continuation Treatment

While there are no systematic studies that answer the question of how long to continue Prozac, panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Nevertheless, patients should be periodically reassessed to determine the need for continued treatment.

HOW SUPPLIED

The following products are manufactured by Eli Lilly and Company for Dista Products Company.

Prozac® Pulvules®, USP, are available in:

The 10-mg[1] Pulvule is opaque green and green, imprinted with DISTA 3104 on the cap and Prozac 10 mg on the body:

NDC 0777-3104-02 (PU3104[2]) – Bottles of 100
NDC 0777-3104-07 (PU3104[2]) – Bottles of 2000
NDC 0777-3104-82 (PU3104[2]) – 20 FlexPak™[3] blister cards of 31

The 20-mg[1] Pulvule is an opaque green cap and off-white body, imprinted with DISTA 3105 on the cap and Prozac 20 mg on the body:

NDC 0777-3105-30 (PU3105[2]) – Bottles of 30
NDC 0777-3105-02 (PU3105[2]) – Bottles of 100
NDC 0777-3105-07 (PU3105[2]) – Bottles of 2000
NDC 0777-3105-33 (PU3105[2]) – (ID[4]100) Blisters
NDC 0777-3105-82 (PU3105[2]) – 20 FlexPak™[3] blister cards of 31

The 40-mg[1] Pulvule is an opaque green cap and opaque orange body, imprinted with DISTA 3107 on the cap and Prozac 40 mg on the body:

NDC 0777-3107-30 (PU3107[2]) – Bottles of 30

Liquid, Oral Solution is available in:

20 mg[1] per 5 mL with mint flavor:

NDC 0777-5120-58 (MS-5120[5]) – Bottles of 120 mL

The following products are manufactured and distributed by Eli Lilly and Company.

Prozac® Tablets are available in:

The 10-mg[1] tablet is green, elliptical shaped, and scored, with PROZAC 10 debossed on opposite side of score.

NDC 0002-4006-30 (TA4006) – Bottles of 30
NDC 0002-4006-02 (TA4006) – Bottles of 100

Prozac® Weekly™ Capsules are available in:

The 90-mg[1] capsule is an opaque green cap and clear body containing discretely visible white pellets through the clear body of the capsule, imprinted with Lilly on the cap and 3004 and 90 mg on the body.

NDC 0002-3004-75 (PU3004) – Blister package of 4

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[1]Fluoxetine base equivalent.
[2]Protect from light.
[3]FlexPak™ (flexible blister card, Lilly).
[4]Identi-Dose® (unit dose medication, Lilly).
[5]Dispense in a tight, light resistant container.

Store at Controlled Room Temperature, 15° to 30°C (59° to 86°F).

ANIMAL TOXICOLOGY

Phospholipids are increased in some tissues of mice, rats, and dogs given fluoxetine chronically. This effect is reversible after cessation of fluoxetine treatment. Phospholipid accumulation in animals has been observed with many cationic amphiphilic drugs, including fenfluramine, imipramine, and ranitidine. The significance of this effect in humans is unknown.

Literature revised January 3, 2003

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ORIGINAL CONTRIBUTION

Paroxetine Controlled Release in the Treatment of Menopausal Hot Flashes

A Randomized Controlled Trial

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Katherine L. Beebe, PhD
Malini Iyengar, PhD
Eric Dube PhD

Context Standard therapy for hot flashes has been hormone replacement with estradiol or progestational agents, but recent data suggest that antidepressants inhibiting serotonin reuptake may also be effective.

Objective To evaluate a selective serotonin reuptake inhibitor (paroxetine controlled release [CR]) in treating the vasomotor symptoms displayed by a general cross-section of menopausal women.

Design and Setting Randomized, double-blind, placebo-controlled, parallel group study conducted across 17 US sites, including urban, suburban, and rural clinics.

Patients A total of 165 menopausal women aged 18 years or older experiencing at least 2 to 3 daily hot flashes and must have discontinued any hormone replacement therapy for at least 6 weeks. Women were excluded if they had any signs of active cancer or were undergoing chemotherapy or radiation therapy.

Intervention After a 1-week placebo run-in phase, study participants were randomized to receive placebo or receive 12.5 mg/d or 25.0 mg/d of paroxetine CR (in a 1:1:1 ratio) for 6 weeks.

Main Outcome Measures Mean change from baseline to week 6 in the daily hot flash composite score (frequency × severity).

Results Fifty-six participants were randomly assigned to receive placebo and 51 to receive 12.5 mg/d and 58 to receive 25.0 mg/d of paroxetine CR. The mean reductions in the hot flash frequency composite score from baseline to week 6 were statistically significantly greater for those receiving paroxetine CR than for those receiving placebo. By week 6, the mean daily hot flash frequency went from 7.1 to 3.8 (mean reduction, 3.3) for those in the 12.5-mg/d and from 6.4 to 3.2 (mean reduction, 3.2) for those in the 25-mg/d paroxetine CR groups and from 6.6 to 4.8 (mean reduction, 1.8) for those in the placebo group. Mean placebo-adjusted reduction in hot flash composite scores were −4.7 (95% confidence interval, −8.1 to −1.3; $P=.007$) comparing 12.5-mg/d paroxetine CR with placebo; and −3.6 (95% confidence interval, −6.8 to −0.4; $P=.03$) comparing 25.0-mg/d paroxetine CR with placebo. This corresponded to median reductions of 62.2% for those in the 12.5-mg/d and 64.6% for those in the 25.0-mg/d paroxetine CR groups compared with 37.8% for those in the placebo group.

Conclusion Paroxetine CR may be an effective and acceptable alternative to hormone replacement and other therapies in treating menopausal hot flash symptoms.

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FOR MANY YEARS, HORMONE REplacement therapy (HRT) with combined estrogen/progestin has been the standard therapy for women experiencing menopausal symptoms. However, increased risks of long-term adverse clinical outcomes in a recent prospective study conducted by the Women's Health Initiative (WHI) on long-term HRT use, are likely to change clinical practice significantly.[1] The long-term benefits of HRT regimens have been called into question; thus, alternative treatments are needed.

Hot flashes are the most common complaint among women entering menopause and, for many women, may continue to occur for up to 5 years (although about 20% of women may have them for up to 15 years).[2] Approximately 75% of perimenopausal women will experience some hot flashes, with 10% to 20% of those enduring severe symptoms.[3] Based on these figures, today more than 25 million women in the United States alone may have experienced symptoms, of which 4 million women reported severe symptoms.[4] Despite this prevalence, the physiology of hot flashes is not fully understood although a disturbance in normal thermoregulatory function is thought to be the main underlying cause. The pri-

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Financial Disclosure: Dr Stearns has served as a consultant to GlaxoSmithKline Pharmaceuticals and Drs Beebe, Iyengar and Dube are employees of GlaxoSmithKline and as employees have stock options in GlaxoSmithKline.
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mary symptom is a subjective and transient sensation of heat that usually lasts 4 to 10 minutes, which may be accompanied by differing degrees of flushing, palpitations, anxiety, irritability, and panic, a rare occurrence.[2]

Women who undergo chemotherapy for breast cancer or who are subsequently prescribed antiestrogens such as tamoxifen may have a 2- to 3-fold increased risk of developing hot flashes.[5-7] However, there has been a reluctance to use the current standard therapy, estrogen, in treating menopausal symptoms of women with a prior breast cancer or in treating those having a high risk of developing breast cancer. The reluctance to use estrogen to treat patients with breast cancer has also extended to progestogens, despite their proven efficacy (low-dose megestrol acetate has been shown to reduce hot flashes by about 80%).[8] Furthermore, the recent data from the WHI indicate that this concern may be justified. In this 5.2-year follow-up study of more than 16 000 healthy postmenopausal women receiving combined estrogen (0.625 mg/d) and progestin (medroxyprogesterone acetate, 2.5 mg/d), the overall health risks appeared to exceed the benefits. The absolute excess risks per 10 000 person-years were 7 more coronary events, 8 more strokes, 8 more pulmonary embolisms, and 8 more invasive breast cancers vs reductions of 6 fewer colorectal cancers and 5 fewer hip fractures.[1] These data suggest that, in the long-term, replacement strategies offer little improvement on normal ovarian aging other than to ameliorate vasomotor symptoms and vulvovaginal atrophy.[9]

The perceived limitations of HRT, coupled with the lack of efficacy and adverse effects observed with nonhormonal therapies, have led clinicians to search for other treatment options. Recent studies of venlafaxine and fluoxetine in women with a prior history of breast cancer have suggested that certain antidepressants with the ability to inhibit serotonin reuptake may significantly reduce vasomotor symptoms of menopause.[10-12] The clinical benefit of these antidepressants is not as great as that observed for estrogen; however, the benefit appears to be greater than what is offered from other nonhormonal pharmacological approaches[13] and from nonpharmacologic approaches such as vitamin E.[14]

The pilot study that my colleagues and I conducted[12] demonstrated that 5 weeks of treatment with immediate-release paroxetine (20 mg/d) reduced the hot-flash composite score of breast cancer survivors by 75%, suggesting that further investigation was warranted. We conducted what is, to our knowledge, the first study of a selective serotonin reuptake inhibitor (SSRI) (paroxetine controlled release [CR]) in treating the menopausal vasomotor symptoms displayed by a group of women who were not primarily breast cancer survivors. We selected paroxetine CR for this study because it is a better tolerated formulation that has lower rates of early discontinuation due to adverse events.[15]

METHODS

Patients

Patients recruited to the study were menopausal women aged 18 years or older who had been: amenorrheic for at least 12 consecutive months, amenorrheic for 6 months but met the biochemical criteria for menopause (follicle-stimulating hormone >40 mIIU/mL and estradiol <20 pg/mL [69.34 pmol/L]), or had undergone bilateral oophorectomy at least 6 weeks before screening. To be included in the study, patients also must have experienced a minimum of 2 to 3 daily hot flashes or at least 14 bothersome hot flashes per week and must have discontinued any HRT at least 6 weeks before screening. Psychotropic drugs must have been discontinued for a specified period prior to screening: 2 weeks for tricyclic antidepressants, selective noradrenaline reuptake inhibitors, SSRIs (other than fluoxetine), lithium and oral neuroleptics, all sedatives and hypnotics; 4 weeks for fluoxetine and monoamine oxidase inhibitors; 12 weeks for depot neuroleptics.

Women were excluded from the study if they presented with signs of an active cancer or were receiving current chemotherapy or radiation therapy. Treatment with selective estrogen receptor modulators (SERMs, eg, tamoxifen) was permitted on the condition that therapy had been initiated at least 3 months before screening and that the dose remained unchanged throughout the study. Other grounds for exclusion were: an active psychiatric disorder, concurrent major depression, intolerance to SSRIs, and substance dependence.

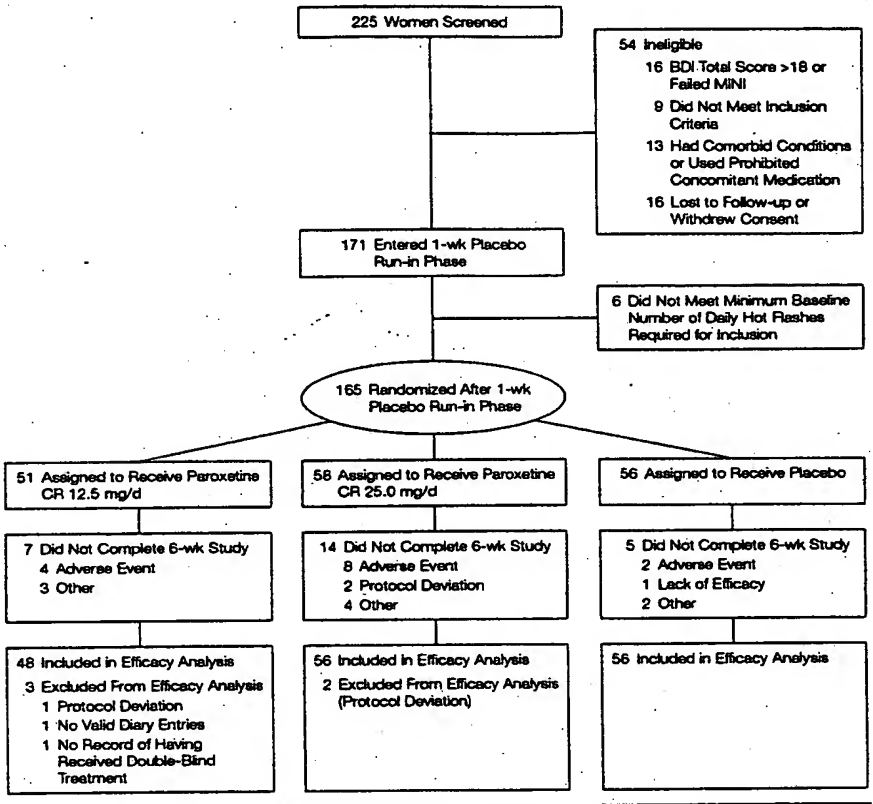
Institutional review board–approved written informed consent was obtained from all patients, and the study was conducted in accordance with the Declaration of Helsinki, 1996 (South Africa amendment). Before starting the study medication, medical histories were taken and physical examinations were performed for each woman. Other evaluations included vital signs, electrocardiogram, Mini International Neuropsychiatric Inventory (MINI),[16] and the Beck Depression Inventory II (BDI-II).[17] Patients with clinically significant mood or anxiety symptoms were excluded to permit the independent examination of the effect of paroxetine CR on vasomotor symptoms.

Design and Procedures

This was a double-blind, placebo-controlled, parallel group study conducted in 17 US sites, including urban, suburban, and rural clinics. Recruitment techniques included newspaper advertisements, presentations to women's groups, and professional referral networks. After the initial screening visit, patients entered a 1-week single-blind, placebo run-in phase to obtain baseline diary data (hot flash frequency and severity) to ensure that each woman met the minimum eligibility criteria, and to screen out any potentially high-placebo responders and thereby exclude those women who would not necessarily benefit from pharmacological intervention. A baseline visit was scheduled to confirm eligibility within 2 days of completing the

run-in phase, after which patients were randomized to receive placebo or to receive 12.5 mg/d or 25.0 mg/d of paroxetine CR (in a 1:1:1 ratio) for the 6-week, double-blind treatment phase (FIGURE 1). Study visits were scheduled for 1, 3, and 6 weeks. Symptom-assessment questionnaires were administered at each visit, and adverse events and vital signs were monitored. At the end of the study period, patients were treated at the discretion of their health care professional.

Figure 1. Patient Flow Chart



BDI indicates Black Depression Inventory; MINI, Mini International Neuropsychiatric Inventory.

Daily Diaries and Symptom-Assessment Questionnaires

Daily hot flash diaries, as developed and validated previously[8,14,16,19] were used to document the frequency and severity of hot flashes at baseline and during weeks 1 through 6 of the study. Hot flash composite scores were calculated from the product of the daily frequency and severity ratings.[18]

Questionnaires (administered at weeks 1, 3, and 6) were used to assess symptoms and problems commonly related to the menopause and potential adverse reactions to study treatment. The BDI-II (21 items) was used both to screen for patients with major depression and to monitor depression during the study. A second instrument, the MINI, was used as a screening tool to prevent patients with primary psychiatric disorders (requiring treatment) from entering the study.

In terms of symptom measurement, the Greene Climacteric Scale (GCS, 21 items) was used to assess core menopausal symptom severity including hot flashes, night sweats, somatic symptoms, and sexual interest. A separate measure, the sleep disturbance visual analog scale (VAS) was used to assess sleep disturbance in the preceding week. Anxiety (eg, feeling dizzy or lightheaded, nervous or having difficulty breathing) was measured via the Beck Anxiety Inventory-II (BAI-II, 21 items). General disability was monitored using the Sheehan Disability Scale total score and scores on the work, social life and leisure activities, and family life and home responsibilities subscores. The Clinical Global Impression (CGI) global improvement item was used to measure the overall improvement from baseline in patients' health.

End Points

The primary objective of this study was to compare the mean change from baseline to week 6 in the daily hot flash composite score among women taking 25.0 mg/d of paroxetine CR with those taking placebo. Secondary objectives of this study were to compare the mean change from baseline to week 6 in the daily hot flash composite score of those taking 12.5 mg/d of paroxetine CR with those taking placebo, and to assess the safety and tolerability of paroxetine CR in the treatment of hot flashes associated with menopause. The composite score was calculated by assigning a number to the severity of the hot flash (mild=1, moderate=2, severe=3, very severe=4) and multiplying by the daily number of hot flashes experienced at that severity level.[18] The 4 resulting numbers were added to give a daily score, and each mean daily score was calculated over the 7 days preceding the latest dose of the study medication.

Other secondary end points included the mean weekly change in hot flash score for weeks 1 through 6, the proportion of hot flash score responders (≥50% reduction in score at study end), the mean change from baseline in questionnaire score (BDI-II, BAI-II, GCS, sleep disturbance VAS, Sheehan Disability Scale), and the proportion of CGI responders (patients achieving a score of 1 or 2 on the clinician-rated CGI global improvement item). Paroxetine CR tolerability was assessed

throughout the study by vital sign and adverse event monitoring.

Statistics

A sample size of 150 women was necessary to give the study 85% power to detect a difference of 3 points between 25.0 mg/d paroxetine CR and placebo (type I error = .05) in the mean change from baseline in daily hot flash composite score, with an SD of 5 points. For the generation of the randomization list, a randomized block of size 6 for the 3 treatments (to achieve a balance) in a 1:1:1 ratio was used. Stratification was not used in this trial. Each site registered in the trial received drugs for a maximum of 36 patients based on this randomization list (6 blocks of random numbers corresponding to the 3 treatments were reserved per site.) The efficacy analyses were performed on all patients who received at least 1 dose of the study medication. Where appropriate, data were assessed for normality and homogeneity, and the last observation carried forward procedure was used to impute missing data. Primary analyses were adjusted for treatment and site and were based on a 2-sided hypothesis at the 5% significance level. No adjustment was made for multiple comparisons. All continuous efficacy variables were analyzed using parametric analysis of variance with treatment and site effects. The proportion of responders was analyzed by a logistic regression model with treatment and site effects. All analyses were performed using SAS statistical software, version 6.12 (SAS Inc, Cary, NC).

Table 1. Patient Demographics*

Characteristics	Paroxetine Controlled Release 12.5 mg/d (n = 51)	Paroxetine Controlled Release 25 mg/d (n = 58)	Placebo (n = 56)
Age group, No. (%), y			
18-34	0	0	0
35-44	4 (7.8)	3 (5.2)	4 (7.1)
45-54	27 (52.9)	29 (50.0)	32 (57.1)
55-64	16 (31.4)	19 (32.8)	17 (30.4)
>64	4 (7.8)	7 (12.1)	3 (5.4)
Age, mean (range), y	53.6 (41-76)	55.0 (39-76)	53.6 (36-68)
Race, No. (%)			
White	44 (86.3)	51 (87.9)	49 (87.5)
Black	6 (11.8)	7 (12.1)	6 (10.7)
Asian	0	0	1 (1.8)
Other	1 (2.0)	0	0
Marital status, No. (%)			
Married	34 (66.7)	34 (58.6)	43 (76.8)
Divorced	7 (13.7)	17 (29.3)	8 (14.3)
Separated	1 (2.0)	0	2 (3.6)
Single	9 (17.6)	7 (12.1)	3 (5.4)
Menopausal history, No. (%)			
Amenorrheic for ≥12 mo	42 (82.4)	46 (79.3)	41 (73.2)
Amenorrheic for 6-11 mo	5 (9.8)	6 (10.3)	9 (16.1)
Ovariectomized ≥6 wk prior to screening	9 (17.6)	7 (12.1)	9 (16.1)
Relevant medical history			
Breast cancer history	2 (3.9)	6 (10.3)	4 (7.1)
Hysterectomy	19 (37.3)	12 (20.7)	19 (33.9)
Hot flash severity at baseline			
Mean daily hot flash frequency	7.1	6.4	6.6
Mean hot flash composite score	16.5	13.6	14.2
Months since onset of hot flash, No. (%)			
1-6	5 (9.8)	8 (13.8)	4 (7.1)
7-12	3 (5.9)	3 (5.2)	8 (14.3)
>12	43 (84.3)	47 (81.0)	44 (78.6)
Concurrent medication, No. (%)			
Tamoxifen	0	4 (6.9)	3 (5.4)
Raloxifene	1 (2)	1 (1.7)	3 (5.4)
Vitamin E	6 (11.8)	12 (20.7)	6 (10.7)
Mean BDI-II total score (range)	3.2 (0-16)	2.3 (0-18)	3.5 (0-14)
Mean BAI-II total score (range)	5.7 (0-21)	4.9 (0-17)	6.0 (0-17)

Abbreviations: BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory.
*Some of the percentages may not sum to 100 due to rounding.

RESULTS

From October 2001 to March 2002, 225 women were screened to enter the placebo run-in phase of the study, and 171 entered the placebo run-in period. Of these, 6 women did not meet the required daily number of hot flashes for study entry; thus, 165 were randomized to receive treatment (Figure 1). There were no exclusions on the basis of placebo effect during the run-in. In all, 139 (84.2%) of 165 of the participants randomized completed the 6-week treatment phase. Withdrawals included 14 women who discontinued study medication due to adverse effects (2 placebo, 12 paroxetine CR), and 1 woman receiving placebo discontinued due to lack of efficacy.

The 3 treatment groups were well matched in terms of patient characteristics (TABLE 1). Unlike previous studies, this was a general population of women, with only 12 (7.3%) with a history of breast cancer. The aim of this study was to examine the effect of paroxetine CR on vasomotor symptoms alone, which is supported by the fact that only 17 patients met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*) criteria for psychiatric disorders, as assessed by the MINI (6 paroxetine CR, 11 placebo). In all, 95.2% had 12 or more years of education and 81.2% experienced hot flashes for 12 months or more. Only 7 patients were receiving concurrent tamoxifen treatment and 5 reported concurrent raloxifene use.

Reduction in Hot Flashes

There were mean reductions from baseline to week 6 in daily hot flash composite score of 8.4 and 7.2 for those taking 12.5 mg/d and 25.0 mg/d of paroxetine CR, respectively (FIGURE 2). Both treatment groups showed a significant benefit of paroxetine CR over placebo. The mean last observation carried forward placebo-adjusted reductions for paroxetine CR were −4.7 (95% confidence interval [CI] −8.1 to −1.3; $P=.007$ vs placebo) and −3.6 (95% CI, −6.8 to −0.4; $P=.03$ vs placebo) for the 12.5-mg/d and 25.0-mg/d groups, respectively. After 6 weeks of treatment, the hot flash composite score was reduced by 62.2% and 64.6% for the lower- and higher-dose paroxetine CR groups compared with a 37.8% reduction for placebo. In a separate analysis, this treatment difference remained even after adjustment for age, disease history (breast cancer or psychiatric disorders), or antiestrogen use.

Compared with placebo, the mean weekly change in hot flash composite score showed that significant improvements that continued to study end were evident within a week of treatment for those taking 25.0 mg/d of paroxetine CR. However, for those taking 12.5 mg/d of paroxetine CR, the mean reduction in the hot flash composite score compared with placebo was statistically significant in weeks 1, 3, 5, and 6 (FIGURE 3). The mean baseline hot flash composite scores were 16.5 (paroxetine CR 12.5 mg/d), 13.6 (paroxetine CR 25.0 mg/d), and 14.2 (placebo). Although the mean reduction from baseline at week 6 appears greater for those receiving 12.5 mg/d of paroxetine CR, the difference in baseline scores means that a smaller percentage reduction was seen among those in the lower dosage group.

By week 6, the mean daily hot flash frequency decreased from 7.1 to 3.8 (mean reduction, 3.3) for those in the 12.5-mg/d and from 6.4 to 3.2 (mean reduction, 3.2) for those in the 25-mg/d paroxetine CR groups and from 6.6 to 4.8 (mean reduction, 1.8) for those in the placebo group. The adjusted mean differences for 12.5 mg/d and 25.0 mg/d of paroxetine CR are −1.55 (95% CI, −2.75 to −0.34; $P=.01$) and −1.50 (95% CI, −2.66 to, −0.34; $P=.01$), respectively. Of 104 women with baseline and week 6 values who received paroxetine CR, more than half experienced a 50% or more reduction in hot flash frequency and severity and were considered responders. The response rates were 58.3% for those receiving 12.5 mg/d and 62.5% for those receiving 25.0 mg/d of paroxetine CR compared with 42.9% of those receiving placebo. The odds of being a responder while taking 12.5 mg/d of paroxetine CR were almost twice that of those taking placebo (odds ratio [OR], 1.95; 95% CI, 0.86-4.40; $P=.111$). Furthermore, the odds of achieving a response were more than 2.5 times greater for women receiving 25.0 mg/d of paroxetine CR than for those receiving placebo (OR, 2.56; 95% CI, 1.15-5.68; $P=.02$).

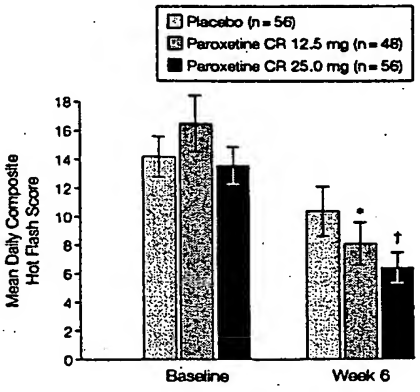
Symptom and Disability Scores

The improvements in hot flash symptoms among those taking paroxetine CR were independent of any significant changes in mood or anxiety symptoms, as shown by symptom-assessment questionnaire scores (TABLE 2). By week 6 the GCS total score improved by 2.0 points for those in the 12.5-mg/d and 3.3 points for those in the 25.0-mg/d paroxetine CR groups, mainly due to a significant improvement in vasomotor symptoms. Scores on the GCS item for sexual interest were minimally changed for all treatment groups after 6 weeks of treatment. In addition, more than 50% of patients in each of the paroxetine CR treatment groups were considered responders as assessed by the CGI global improvement rating. The odds of being a CGI responder were 4.39 (95% CI, 1.78-10.84) times greater for those in the 12.5-mg/d and 4.33 (95% CI, 2.16-10.54) times greater for those in the 25.0-mg/d paroxetine CR groups than for those in the placebo group ($P=.001$).

Tolerability

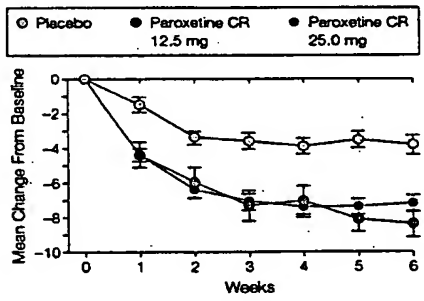
A total of 30 patients (53.6%) receiving placebo reported an adverse event during the study, compared with 63 patients (58.3%) randomized to receive paroxetine CR. Events experienced by patients receiving active treatment were in line with the known tolerability profile of paroxetine CR. The most frequently reported events for paroxetine CR were headache, nausea, and insomnia (TABLE 3) with fewer reports overall from patients receiving the lower dose of paroxetine CR. In both

Figure 2. Change in Daily Composite Hot Flash Scores



Error bars indicate SE.
*P = .03 vs placebo (95% confidence interval [CI] for mean difference, −6.8 to −0.4).
†P = .007 vs placebo (95% CI for mean difference, −8.1 to −1.3).

Figure 3. Change in Weekly Composite Hot Flash Scores



Error bars indicate SE. Compared with placebo, the mean reduction in the hot flash composite score for those taking 25.0 mg/d of paroxetine CR was statistically significant ($P<.05$ in weeks 1, 2, 3, and 4; $P<.001$ in weeks 5 and 6); for those taking 12.5 mg/d of paroxetine CR, the mean reduction in the hot flash composite score was statistically significant in weeks 1, 3, and 6 ($P<.05$) and in week 5 ($P<.001$).

Table 2. Change From Baseline to 6 Weeks in Menopause-Related Symptoms and General Impairment

Measure*	Paroxetine Controlled Release, mg/d			Adjusted Mean Difference From Baseline (SE)			Placebo-Adjusted Mean Difference			
				Paroxetine Controlled Release, mg/d			Paroxetine Controlled Release, 12.5 mg/d		Paroxetine Controlled Release, 25.0 mg/d†	
	12.5	25.0†	Placebo	12.5	25.0†	Placebo	Adjusted Mean Difference From Baseline (95% CI)	*P* Value	Adjusted Mean Difference From Baseline (95% CI)	*P* Value
Composite hot flash score	16.5	13.6	14.2	−8.52 (1.27)	−7.43 (1.18)	−3.82 (1.17)	−4.7 (−8.1 to −1.3)	.007	−3.6 (−6.8 to −0.4)	.03
Depression (BDI-II)‡	3.2	2.3	3.5	−0.73 (0.49)	−0.06 (0.47)	−0.33 (0.45)	−0.4 (−1.7 to 0.9)	.55	0.3 (−1.0 to 1.5)	.68
Anxiety (BAI-II)	5.7	4.9	6.0	−1.63 (0.64)	−1.23 (0.61)	−1.11 (0.59)	−0.5 (−2.2 to 1.2)	.55	−0.1 (−1.8 to 1.5)	.86
Vasomotor symptoms (GCS)	3.7	3.4	3.4	−1.75 (0.24)	−1.55 (0.23)	−0.83 (0.22)	−0.9 (−1.6 to −0.3)	.005	−0.7 (−1.3 to −0.1)	.02
Sexual interest (GCS)	0.4	0.4	0.5	−0.02 (0.11)	−0.02 (0.10)	−0.07 (0.10)	0 (−0.2 to 0.3)	.73	0.1 (−0.2 to 0.3)	.71
Sleep (sleep disturbance VAS)	4.3	4.3	4.33	−1.38 (0.36)	−1.60 (0.35)	−1.10 (0.33)	−0.3 (−1.2 to 0.7)	.56	−0.5 (−1.4 to 0.4)	.29
Disability (SDS)†	1.8	1.2	2.3	−0.83 (0.54)	0.01 (0.52)	0.06 (0.50)	−0.9 (−2.3 to 0.5)	.22	−0.1 (−1.5 to 1.4)	.94

Abbreviations: BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; CI, confidence interval; GCS, Greene Climacteric Scale; SDS, Sheehan Disability Scale; VAS, visual analog scale.
*Reduction from baseline score represents an improvement. The BDI-II, BAI-II, and GCS include 21 items rated on 4-point scales where 0 is the most positive score and 3 is the most negative. The Sleep Disturbance VAS ranges from 0 (none) to 10 (severe). The SDS has 3 subscales each consisting of a VAS ranging from 0 (not at all) to 10 (very severely).
†Total score.
‡For SDS only 50 patients receiving 25 mg/d of paroxetine were evaluable. One patient lacked a baseline value.

Table 3. Most Frequently Reported Adverse Events by at Least 5% of Patients in Any Treatment Group*

Adverse Event	Paroxetine Controlled Release				Placebo
	No. (%) of Patients Taking 12.5 mg/d (n = 50)†	*P* Value	No. (%) of Patients Taking 25.0 mg/d (n = 58)	*P* Value	No. (%) of Patients Taking Placebo (n = 56)
Headache	5 (10.0)	.92	9 (15.5)	.85	7 (12.5)
Dizziness	4 (8.0)	.19	5 (8.6)	.21	1 (1.8)
Nausea	3 (6.0)	.34	7 (12.1)	.06	1 (1.8)
Dyspepsia	3 (6.0)	.10	2 (3.4)	.50	0
Insomnia	2 (4.0)	.60	6 (10.3)	.11	1 (1.8)
Constipation	1 (2.0)	.47	4 (6.9)	.12	0
Lethargy	0		4 (6.9)	.12	0
Somnolence	0		4 (6.9)	.36	1 (1.8)

*All *P* values are for the comparison of paroxetine controlled release and placebo and were calculated using Fisher exact test, with the exception of headache for which the χ^2 test was used.
†One patient had no record of having received double-blind treatment.

dose groups, the majority of adverse events reported were mild or moderate in severity (approximately 89%). Ten (20%) of 50 patients receiving 12.5 mg/d and 18 (31%) receiving 25.0 mg/d of paroxetine CR experienced adverse events that were considered possibly or probably related to their medication. Of these patients, a total of 12 (4 in the 12.5-mg/d and 8 in the 25.0-mg/d paroxetine CR groups) did not complete the study.

COMMENT

We have previously demonstrated that the immediate-release formulation of paroxetine may be effective in treating hot flashes and their associated symptoms in women with a history of breast cancer. The purpose of the current study was to determine the extent to which paroxetine CR can relieve hot flashes in a general population of menopausal women. A substantial reduction in hot flash symptoms was observed following 6 weeks of paroxetine CR treatment. Hot flash composite scores were reduced by 62.2% in those receiving 12.5 mg/d and 64.6% in those receiving 25.0 mg/d of paroxetine CR. Although head-to-head comparisons are not available, our results compare favorably with the findings of similar studies for fluoxetine (50% reduction over 4 weeks at 20 mg/d) and venlafaxine (61% reduction over 4 weeks at 75 mg/d and 150 mg/d; 37% over 4 weeks at 37.5 mg/d).[10,11] In our study, absolute reductions in hot flash composite score were similar regardless of paroxetine CR dose level, suggesting that 12.5 mg/d is an adequate and well-tolerated starting dose for most women.

At study end, 63 (60.5%) of 104 women who received paroxetine CR achieved a 50% or greater reduction in their hot flash composite scores. At the start of the study, women were experiencing an average of 6.5 hot flashes per day. By week 6, the average number of daily hot flashes was 3.8 for those in the12.5-mg/d and 3.2 for those in the 25.0-mg/d paroxetine CR groups and 4.8 for those in the placebo group. In addition, 29%, 30%, and 19.6% of women in the respective groups did not experience any hot flashes during week 6. A mean reduction in the hot flash composite score and treatment response showed a consistent pattern among those taking 25.0 mg/d of paroxetine CR. It is reassuring to note that significant improvements over placebo were also seen for paroxetine CR on the CGI and GCS (vasomotor symptoms subscore) questionnaires, since

they assess symptoms that overlap with those detected by the primary efficacy measure. In addition, the CGI is a clinician-rated measure in contrast to the patient-assessed hot flash score. The odds of being rated as improved or very much improved on the CGI were around 4 times greater for patients receiving paroxetine CR than for those receiving placebo. Taken together with the findings of the WHI, these data suggest that paroxetine CR may have a place in the treatment armamentarium for women experiencing hot flashes.

As in studies of related agents,[10,11] these central efficacy findings are largely independent of any effect that paroxetine CR may have on mood or anxiety symptoms because patients entering the study were not permitted to have clinically significant disorders of this kind. Furthermore, levels of depression and anxiety were much lower among those participating in our study than what was reported in patients who entered a recent study of fluoxetine in the treatment of hot flashes,[10] and the majority of patients in our study who had such symptoms could be graded at the minimal level by the BDI-II (93%) and BAI-II (78%).

In general, paroxetine CR was well tolerated. Rates of commonly reported adverse events were generally lower than those reported in a recent study examining the use of paroxetine CR in treating a depressed population.[15] Although both doses of paroxetine CR were associated with a similar magnitude of hot flash reduction, the lower dose was better tolerated. Because the slow release of this formulation was associated with a low drop out rate due to adverse events in this depression trial, it could potentially improve compliance and may be particularly suited for mid-term to long-term treatment of menopausal women. The majority of adverse events in our study were mild or moderate and paroxetine CR appeared to have little or no effect on sexual function over 6 weeks. This is in agreement with a previous pilot study of this agent.[12]

The main weakness of this study is that no direct comparisons were made in terms of associated menopausal symptoms such as insomnia. Furthermore, there were low proportions of black and Asian women in the study population, and it is likely that the recruitment methods used for the study did not target particular ethnic groups effectively. Since black women are known to exhibit more severe menopausal symptoms (particularly vasomotor symptoms) and Asian women experience less severe symptoms, it would be interesting to compare treatment responses among different racial groups.[20]

Although surveys such as the Study of Women's Health Across the Nation (SWAN) have greatly expanded our knowledge of the demographic and lifestyle factors affecting the symptoms of menopause, little is still known about the physical basis of hot flashes.[20] Hot flashes are thought to occur as the result of an alteration in the central nervous system thermoregulatory set point caused by falling estrogen levels. However, the basis for the beneficial effect of SSRIs on vasomotor symptoms remains unknown. Evidence from animal studies suggests that serotonin (5-HT) plays an important role in thermoregulation and that the temperature increases associated with hot flashes could be linked to an overloading of serotonin receptor sites in the hypothalamus.[21-23] Two 5-HT receptor subtypes, 5-HT1a and 5-HT2a, have been closely associated with temperature control in mammals.[24] These receptors appear to have opposite effects on temperature regulation, with 5-HT2a mediating hyperthermic effects and 5-HT1a mediating hypothermic effects.[13] It is likely that a balance between these 2 receptors is important in maintaining optimal thermoregulation. Notably, the expression and activity of 5-HT receptors can be modulated by gonadal hormones and adrenal corticosteroids, and this may be the functional link between some of the hormonal systems linked to hot flashes and serotonin.[25,26] Further work is needed to clarify the mechanisms behind hot flashes and to explain fully the mode of action of current therapies.

This study provides new information on the treatment of hot flashes. Based on these results and the preceding pilot trial of Stearns and colleagues,[12] paroxetine CR is a well-tolerated alternative to HRT and other therapies in the treatment of hot flash symptoms. However, the duration of benefit of paroxetine CR in treating menopausal hot flashes and its applicability as a first-line or second-line treatment remain unknown. Furthermore, the question remains of whether women who are resistant to 1 antidepressant will respond to another. The optimal dose for treating hot flashes also remains to be determined and may be lower than that recommended in depression.

Author Contributions: As principal investigator, Dr Stearns had full access to the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Stearns, Beebe, Iyengar.
Acquisition of data: Beebe.
Analysis and interpretation of data: Stearns, Beebe, Iyengar, Dube.
Drafting of the manuscript: Stearns, Beebe, Iyengar, Dube.
Critical revision of the manuscript for important intellectual content: Beebe, Iyengar, Dube.
Statistical expertise: Beebe, Iyengar, Dube.
Obtained funding: Beebe.
Administrative, technical, or material support: Dube.
Study supervision: Stearns, Beebe, Dube.
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> The man who wishes to remain faithful to justice must make himself continually unfaithful to inexhaustibly triumphant injustice.
> —Charles Péguy (1873-1914)

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Treatment of premature ejaculation with paroxetine hydrochloride.

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AIMS OF THIS STUDY: To evaluate the efficacy of chronic and 'on demand' administration of paroxetine hydrochloride in the drug treatment of premature ejaculation (PE). MATERIALS AND METHODS: Ninety-four normally potent men, aged 18-61 y (mean 39 y) with premature ejaculation were treated between January 1996 and March 1997, with oral paroxetine hydrochloride, a selective serotonin re-uptake inhibitor (SSRI). All men were either married or in a stable relationship. Sixty-four out of ninety-four men (Group A) were initially treated with paroxetine hydrochloride 20 mg administered once daily. Those men who responded with improved ejaculatory control within four weeks, were then treated with 'on-demand' paroxetine hydrochloride (20 mg) administered 3-4 h prior to planned intercourse. The remaining 33 out of 94 men (Group B) were initially treated with 'on-demand' paroxetine hydrochloride 20 mg administered 3-4 h prior to planned intercourse. RESULTS: The mean pre-treatment ejaculatory latency time (ELT) of both group A and B was 0.4 min (range 0-1 min) in 205 intercourses at a frequency of 0.4 intercourses per week. In group A after four weeks of daily administration of paroxetine, the mean ELT was 4.5 min (range 1-anejac.) in 761 intercourses at a frequency of 2.4 intercourses per week. Fifty-three out of sixty-one men in group A regarded their ejaculatory control as improved and were then treated with 'on-demand' paroxetine, achieving an ELT of 3.9 min (range 0-10) in 608 intercourses at a frequency of 2.6 intercourses per week. Thirty-six men in this group of 53 regarded that they had maintained improved ejaculatory control with a mean ELT of 5.5 min (range 2-20 min) after a further four weeks of treatment ($P < 0.001$). The remaining 17 men reported a recurrence of poor ejaculatory control with a mean ELT of 0.7 min (range 0-2 min). In group B with initial 'on-demand' paroxetine after a mean of 4.5 weeks of treatment, the mean ELT was 1.5 min (range 0-5 min) in 298 intercourses at a frequency of 2.2 intercourses per week. Adverse effects were only recorded in men taking daily paroxetine and included anejaculation in 5 out of 61, inhibited orgasm in 3 out of 61 and reduced libido on 3 out of 61. Erectile dysfunction was not reported and 'on demand' paroxetine was not associated with any adverse effects. CONCLUSIONS: Paroxetine hydrochloride appears to be a useful agent in the pharmacological treatment of premature ejaculation when administered on a chronic, an 'on-demand' basis following chronic treatment or initial 'on demand' basis.

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nature publishing group

The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study.

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BACKGROUND: Despite the limited number of available study comparing of their efficacy, selective serotonin re-uptake inhibitors (SSRI) have been thought to have beneficial effects for the patients with premature ejaculation. In the present study, we decided to examine the efficacy of citalopram, an SSRI, in the treatment of premature ejaculation. METHOD: The study was consisted of 26 married patients diagnosed with premature ejaculation according to Diagnostic and Statistical Manual of Mental Disorders Third Revised Version (DSM-III-R). The patients were randomly assigned to two groups, citalopram (group I) and placebo (group II), each consisting of 13 patients. The effects of drug on the ejaculatory function were assessed by the intravaginal ejaculation latency time. Additionally, all patients were screened by using Clinical Global Impression-Improvement Scale (CGI-I) and Yonsei Sexual Function Inventory-II (YSFI-II). RESULTS: The increase in the intravaginal ejaculation latency time in the citalopram group was statistically significant than that of placebo group. In addition, with respect to the subscales of the YSFI-II scale, similar overall significant improvements were seen in the patients given citalopram compared to those given placebo. Of group I patients, five (38.5%) were considered as 'very much improved' and four (30.8%) 'much improved' by CGI-I and only one of group II patients (7.7%) showed 'much improved'. CONCLUSION: The patients treated with citalopram showed significantly greater improvement compared to the patients receiving placebo.

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I. Early Report

Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment

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Available online 3 September 1997.

II. Summary

III. Background

Major depression affects more than 5% of the population and is a serious health and economic problem. Antidepressants have a slow onset of action and are effective in less than two-thirds of patients. The biochemical effects of selective serotonin reuptake inhibitors may be limited by the negative feedback from serotonin autoreceptors. Pindolol is an antagonist of both serotonin autoreceptors and β-adrenoceptors. We studied the effect of the addition of pindolol to fluoxetine antidepressant treatment.

IV. Methods

Of 132 eligible patients with major depression, 111 were randomly assigned to treatment with fluoxetine (20 mg daily) and either placebo or pindolol (7·5 mg daily). Patients were assessed twice a week for the first 3 weeks of active treatment and then once a week until the end of the study (42 days). Hamilton and Montgomery-Asberg depressionrating scales were used to assess depression severity.

V. Finding

The proportion of patients who responded to treatment with fluoxetine and pindolol was greater than that with fluoxetine and placebo (41/55 [75%] vs 33/56 [59%], [90% CI 1·1–30·1], p=0·04). The proportion of patients who achieved a sustained response was also greater in the fluoxetine and pindolol group than in the fluoxetine and placebo group (38/55 [69%] vs 27/56 [48%] [5·9–35·9], p=0·03). The number of days to reach a sustained response was lower in the fluoxetine and pindolol group than in the fluoxetine and placebo group (median 19 vs 29 days, p=0·01), however, there was no difference in the time-toonset of clinical improvement when stringent conditions were used (15 vs 18 days, p=0·20).

VI. Interpretation

The addition of pindolol to fluoxetine antidepressant treatment increases the effectiveness of fluoxetine therapy. Further work is needed to resolve whether the time to clinical improvement benefits from this combination and whether the increase in efficacy occurs with other antidepressants.

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Augmentation of fluoxetine's antidepressant action by pindolol: analysis of clinical, pharmacokinetic, and methodologic factors.

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In a controlled trial, the beta-adrenoceptor/5-hydroxytryptamine-1A (5-HT1A) receptor antagonist pindolol accelerated and enhanced the antidepressant effect of fluoxetine. The median times to sustained response (> or = 50% reduction of baseline severity maintained until endpoint) were 19 days for fluoxetine plus pindolol (N = 55) and 29 days for fluoxetine plus placebo (N = 56) (p = 0.01). The response rate at endpoint was 16% greater in patients treated with the combination. The plasma concentration of pindolol remained stable between 3 days (first blood sampling) and 6 weeks. Mean values were approximately 26 nM, a concentration higher than the Ki of (-)pindolol for human 5-HT1A autoreceptors (11 nM). Plasma fluoxetine and norfluoxetine concentrations increased steadily until the fourth week of treatment. Fluoxetine concentrations were lower in patients receiving the combination (p = 0.043), but there was no significant relationship to the clinical response in either group. A reanalysis of the data using a survival analysis revealed that significant differences in the time to sustained response between both groups would have also been detected (1) in a 2-week trial, (2) without a placebo lead-in phase, and (3) with less frequent visits. However, the use of "response" instead of "sustained response" as measure of clinically relevant change would have greatly diminished the difference between treatment arms (p = 0.08 instead of p = 0.01). This emphasizes the need of using stringent outcome criteria in antidepressant drug trials. A comparison of the data of all sustained responders (N = 27) in the fluoxetine-plus-placebo group with the first 27 responders in the fluoxetine-plus-pindolol group (of a total of 38) revealed a highly significant difference in the time to sustained response (18 and 10 days, respectively; p = 0.0002). This indicates that the faster response in the fluoxetine-plus-pindolol group is not a result of the greater proportion of responders.

Publication Types:

- Clinical Trial
- Randomized Controlled Trial

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